The world is now facing one of the most devastating public health concerns where the 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is spreading all over the world initiating from Wuhan, China, started from December, 2019. The World Health Organization (WHO) already announced the situation as pandemic all over the world. According to the webpage of WHO, this SARS-CoV-2 has been spreading all over the world (223 countries, areas or territories) with 126,890,643 of confirmed cases and 2,778,619 of confirmed deaths as of March 30, 2021. Accumulated published documents indicate that the SARS-CoV-2 virus primarily affects the lungs causing hypoxia which is the leading cause of death. There are many reports describing that with the progress of this disease, many other organs (such as heart, kidney, liver, brain) of the affected person start to malfunction. Though SARS-CoV-2 uses the cell surface receptor angiotensin-converting enzyme 2 (ACE-2) expressed by lungs, cardiovascular system, kidneys but it is still not clear except lungs all these other organs are directly affected by this virus or not. Therefore, the aim of this review is to gather information about the affected/damaged organs or tissues and the consequences of this damage in the COVID-19 patients.

**Keywords**: ARDS, ACE-2, COVID-19, multi-organ failure, pneumonia, SARS-CoV-2.

**ABSTRACT**

Coronaviruses are a family of related viruses that cause diseases, ranging from mild to lethal, in mammals and birds. In human such type of coronavirus causes deadly pneumonia with other life threatening diseases. The first coronavirus was reported in 1931 but the first human coronavirus (HCoV-229E) was isolated from human in 1965\(^1\). However, five coronaviruses have been reported in different times of this century: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002\(^2,3\), human coronavirus (HCoV-NL63) in 2003\(^4\), coronavirus HKU1 (CoV-HKU1) in 2004\(^5\), Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012\(^6\) and SARS-CoV-2 in 2019\(^7,8\). Among them SARS-CoV-2 (also called the 2019 novel coronavirus, 2019-nCoV) is the coronavirus strain that causes the deadly respiratory illness, severe pneumonia, along with other severe health problems is known as coronavirus disease-19 (COVID-19). Since December 2019 initiating from Wuhan, China, this 2019-nCoV has been spreading all over the world (223 countries, areas or territories) with 126,890,643 of confirmed cases and 2,778,619 of confirmed deaths as of March 30, 2021\(^9\). This situation of the current World is declared as the most crisis situation after World War 2 by World Health Organization (WHO). Though currently some vaccines are approved by WHO and these vaccines are used in different countries all over the world, in many countries where vaccines are inadequate, treatment of COVID-19 largely depends on the usual treatment of pneumonia and the experience of the clinicians\(^10\). Therefore, the aim of this current review is to gather the information about the
complications of patients infected with this novel virus, 2019-nCoV.  

Clinical features  
Persons infected with SARS-CoV-2 showed similar symptoms of normal flu. But the most important clinical feature is the occurrence of severe pneumonia. Within February 2020, three major case studies reported pneumonia as a major clinical feature of patients infected with SARS-CoV-2 in Wuhan, China7,11,12. One study about the clinical manifestations of COVID-19 patients infected with SARS-CoV-2 has been reported. The study reported about 278 COVID-19 patients where all of them were suffering from severe pneumonia. All the patients were older than 18 years and about 61.9% (n=172) were males. Fever was the most common symptom (92.8%; n = 258), followed by cough (69.8%; n = 194), dyspnoea (34.5%; n = 96), myalgia (27.7%; n = 77), headache (7.2%; n = 20) and diarrhoea (6.1%; n = 17).13 However, symptoms of COVID-19 can vary from mild features to critical state. In addition to those that mentioned earlier, the patients may show muscle ache, confusion, headache, sore throat, rhinorrhea, chest pain, sputum production, nausea and vomiting and many others7,11,12. Following different such types of symptoms acute respiratory distress syndrome (ARDS) and multiple-organ failure occurred rapidly, resulting in death within a short period of time14. Patients with underlying conditions like hypertension, cancer, kidney diseases, diabetes and much other comorbidity are more prone to severe respiratory condition and death than normal patients7,11,12. However, as the virus is spreading all over the world, new and new symptoms might occur depending on the changed nature of this virus, physiological status of the patients as well as the region of the world.

Table 1: Summary of the effects of organs/tissues with their corresponding symptoms in the COVID-19 patients all over the Globe.

| Name of the organ/tissue | Expression of ACE-2 | Symptoms of COVID-19 patients | References |
|--------------------------|---------------------|-------------------------------|------------|
| Lungs (alveolus)         | yes, high           | ARDS, pneumonia               | [7], [8], [16], [20], [21] |
| Gastrointestinal system  | yes, high           | diarrhea                      | [17], [20], [34] |
| Blood vessels            | yes, high           | blood coagulation ??          | [16], [42], [43], [44] |
| Heart (myocardium)       | yes, high           | arrhythmia, myocardial damage | [7], [18], [46], [47] |
| Kidney (nephron)         | yes, high           | chronic kidney disease        | [18], [50], [51] |
| Liver (hepatocytes)      | no (yes? low)       | liver injury, abnormal functions | [53], [54] |
| Brain (neuron, glia)     | no (yes???)         | anosmia, ageusia              | [65-67] |

Footnote: ? = non-conclusive, ?? = highly non-conclusive.

The reason behind the occurrence of severe pneumonia (inflammation of the air sacs of lungs) in the SARS-CoV-2 infected persons is that the virus uses the surface protein called angiotensin-converting enzyme 2 (ACE-2)13 and cells of the lungs express this ACE-2 surface receptors16. This ACE-2 cell surface receptor is also expressed by some other cell types such as cells of the gastrointestinal system17, arterial and venous endothelial cells, smooth muscle cells [16], cells of heart, kidney and testes18. Structural study showed that the SARS-CoV-2 binds 10 to 20 times strongly with the human ACE-2 than the SARS-CoV predecessor.19. This might be the reason why this new SARS-CoV-2 is more infectious or contagious than its 2002 predecessor, SARS-CoV. Since a variety of tissues expressed ACE-2 in their cells, these tissues or organs might be affected first and due to the malfunctions of one organ others are affected and as a result the person dies (Figure 1). In the preceding section, we will try to summarize informations found in different articles affecting various vital organs of COVID-19 patients (Table 1):

Lungs  
As the name suggests, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), this virus primarily/mainly affects the respiratory system with severe infection in the lungs. There are a large number of reports of severe pneumonia in COVID-19 patients7,8,20,21. Although much is known about the rate of mortality in COVID-19 patients, less is known about the pathophysiology of this virus. However, accumulating evidences suggest a general mechanism of causing pneumonia22 (Figure 2). According to this article the mechanism starts with the binding of virus to epithelial cells in the nasal cavity and starts replicating. This virus uses the cell surface receptor ACE-2 to bind with the cell21. In the next few days, the virus start to migrate downs the respiratory tract. During this time the body gives a response by activating innate immune response by producing interferons.

One of the interferon that is produced during early phase of infection of SARS is interferon-inducible protein-10, CXCL-10. For this reason CXCL-10 has been reported as a disease marker for SARS patients24. Within a next few days, the virus reaches into the basic structure of the lungs, the alveolus. With the help of this basic structure, the lungs perform its main function which is the exchange of gases (O2 and CO2). Probably, like SARS-CoV, SARS-CoV-2 infects the type-II alveolar cells. Influenza virus also infects the same alveolar cells of the lungs26. Type-II alveolar cells constitute 60% of lung alveolar cells and produce phospholipid rich materials known as surfactant which reduces the surface tension between the two wet
surfaces of the alveolus. As a result alveolus fails to reinflate causing ARDS with body’s excessive defense mechanism. One of the major causes of ARDS and multiple-organ failure is the cytokine storm. The cytokine storm contains a large number of different types of soluble mediators like pro-inflammatory cytokines (IL-1β, IL-6, IL-8, granulocyte-macrophage colony stimulating factor and ROS) and chemokines (CCL2, CCL3, CCL5, IFNγ-induced protein 10) that all contribute to the occurrence of ARDS. Viral replication into the cell causes these pro-inflammatory cytokine or chemokine to release and as a response to this there is the induction of apoptosis in the lung epithelial and endothelial cells involving mechanisms like Fas–Fas ligand(FasL) or TRAIL–death receptor 5 (DR5). Death of lungs epithelial cells and endothelial cells causes damage of pulmonary microvascular and alveolar epithelial cell barriers leading to the formation alveolar edema ultimately causing hypoxia in the body. Therefore, probably, cytokine storm is the cause of forming ARDS in the COVID-19 patients infected with SARS-CoV-2.

Gastrointestinal system

Initially diarrhea or gastrointestinal problems was considered as a minor symptoms of this virus comparing with pneumonia or problems with respiratory systems but with the increasing number of infected cases the incidence of having diarrhea is also increasing. Now, diarrhea is one of the frequent symptoms in COVID-19 infection as it was detected in up to 30% of patients with MERS-CoV and 10.6% of patients with SARS-CoV-2. In addition to use the receptor protein ACE-2 expressed on the cell surface, SARS-CoV also uses the cellular serine proteases (TMPRSS2) to get entry into the cell inside. The entry process into the cells involves priming by TMPRSS2 which allow spike protein cleavage and regulating the entire mechanism. But the major role of entry plays by the surface protein ACE-2 which first mediates the attachment of the virus with the host cell membrane and then TMPRSS2 favors the fusion of the two (one is the virus and other one is the host cell) cell membranes. Therefore, the virus entry into the host cell or infectivity mainly depends on binding with the ACE-2 surface receptor and this ACE-2 surface receptor is also largely expressed by gastrointestinal epithelial cells. Analyses of the COVID-19 patients also confirmed the presence of SARS-CoV-2 RNA in the anal or rectal swabs as well as in the stool specimens. Even after clearance of the virus in the upper respiratory system, SARS-CoV-2 RNA is still found in the anal or rectal swabs. All of these evidences indicate that diarrhea or gastrointestinal abnormalities should be considered as a major symptom of 2019-nCoV infections and absence of SARS-CoV-2 RNA in the anal or rectal swabs or in the stool specimens should take into account before declaring an infected person to be a healthy person.

Blood endothelial cells

ACE-2 surface receptors are expressed in the endothelial cells of blood vessels. Therefore, what will be the consequences of infected endothelial cells of blood vessels has not yet been addressed. However, there are evidences that some COVID-19 patients have prominent changes in blood coagulation. For example, the values of D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen (FIB) in all SARS-CoV-2 cases are substantially higher than those in healthy controls and values of D-dimer and FDP are higher in severe COVID-19 patients than milder patients. And the prothrombin time activity (PT-act) is lower in SARS-CoV-2 patients. In another article, it was also reported that at the late stages of pneumonia caused by SARS-CoV-2, fibrin-related markers (e.g.}

Figure 1: Distribution of SARS-CoV-2 in the COVID-19 patients.
In COVID-19 patients, the SARS-CoV-2 is mainly found in the lungs. Beside lungs, so far reported, this virus is found in the cardiovascular system (a), in the brain (b), in the liver but at low levels (c) and in the gastrointestinal system (d).
D-dimer) markedly elevated suggesting coagulation activation and starting of secondary hyperfibrinolysis which may be induced following severe 2019-nCoV infection. When some (n=99) of severe COVID-19 patients, who had markedly elevated D-dimer, received heparin as anticoagulant therapy for 7 days or longer had better prognosis of the disease with decreased rate of mortality of about 20%. Therefore, changes in the blood coagulation is a prominent features of severe infection with SARS-CoV-2 and it was suggested that monitoring D-dimer and FDP values may be helpful for the early identification of severe cases.

Heart and cardiovascular system
Since myocardium or cardiac muscle cells express ACE-2 surface receptor, the SARS-CoV-2 might attack the heart as well though there is no report about the presence of virus into the heart. In a case study of 138 COVID-19 patients who admitted into the hospital, 16.7% developed arrhythmia and 7.2% presented acute cardiac injury. In another report, acute cardiac injury was reported in 5 among the first 41 humans infected with SARS-CoV-2 in Wuhan, China, with an increased level of high-sensitivity cardiac troponin I. Another acute cardiac injury marker brain-type natriuretic peptide (BNP) was also found to be elevated among patients admitted in hospital ICU in Washington. There is a report of 150 COVID-19 patients from Wuhan, China, where 68 (45%) died. Among 68 patients, 29 (40%) patients died exclusively due to myocardial damage or in combination with myocardial damage and circulatory failure. COVID-19 patients with comorbidity are more prone to die than normal patients. According to the New York State Health Department, among these comorbidities hypertension is number one in terms of patient’s severity. Because hypertensive patients have to use ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and usage of these drugs can increase the ACE-2 expression. Since ACE-2 surface receptors are used by SARS-CoV-2, usage of these anti-hypertensive drugs can be life threatening for a person who has both hypertension and COVID-19. However, Tignanelli et al. claimed that no evidence is available to support routine discontinuation of ACEIs or ARBs in COVID-19 patients since the role of renin-angiotensin system (RAS) inhibition in COVID-19 is controversial. Therefore, they suggest urgent requirement of multicenter trials to test this hypothesis in patients with COVID-19 before the medical community makes recommendations for patients to withhold potentially life-saving drugs.

Kidneys
Though kidneys are expressing ACE-2, there are no reports yet about the presence of SARS-CoV-2 into the kidney like heart. Chronic kidney disease (CKD) is a frequently encountered disease in the general population of a country. During the first two months of the current outbreak in China, CKD was re-reported in 4.3% of the Chinese patients infected with COVID-19 who had severe presentation. End-stage kidney disease patients are a highly susceptible group with an infection rate of 16%, which exceeds that observed in other populations. Persons infected with SARS-CoV-2 with co-morbidity are at the high risk of mortality. And various kidney diseases are vital candidate of this comorbidity. One article concludes that the prevalence of kidney disease on admission and the development of acute kidney disease (AKI) during hospitalization in patients with COVID-19 is high and is associated with in-hospital mortality. Hence, clinicians should increase their awareness of kidney disease in patients with severe COVID-19.

Liver
There are few reports concerning the liver dysfunctions in COVID-19 patients. Though there are no reports yet that hepatocytes express ACE-2 surface receptors, but one article reported that bile duct epithelial cells may
express ACE-2 receptors more than the hepatocytes. In a study of 417 COVID-19 patients, 318 (76.3%) had abnormal liver test results and 90 (21.5%) had liver injury during hospitalization. These abnormal liver tests turned into more pronounced in the next 2 weeks where all the essential liver enzymes (ALT, AST, total bilirubin and γ-GT) elevated to more than 3 times of upper limits indicating abnormal liver tests had higher risks of progressing to severe disease in SARS-CoV-2 infection. In another study of 99 COVID-19 patients in China, 43% patients had differing degrees of liver function abnormality with ALT and AST with an upper range of ALT 7590 U/L and AST 1445 U/L. Opposite state of arguments are also reported concerning liver damage in COVID-19 patients. According to the report the derangement of liver function is mild and when liver function tests for patients with different durations of symptoms are examined, there is no evidence that later presentation is associated with greater liver function derangement. Therefore, SARS-CoV-2 has direct adverse effects on liver function is currently not known due to unavailable data on the expression of viral receptor ACE-2 in the hepatocytes. But according to Guan et al. hepatocytes do express the ACE-2 receptors but at very low concentrations. They also proposed a mechanism how hepatocytes infected by SARS-CoV-2. They reported upon SARS-CoV-2 infection, the upregulation of ACE-2 in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells which express ACE-2 higher than hepatocytes and this might play role in liver damage in COVID-19 patients.

**Brain**

Though the invasions of molecules or particles are strictly regulated into the brain by blood-brain barrier (BBB), many viruses (from human immunodeficiency virus type 1 to togaviruses) can escape the BBB by different mechanisms and enter into the brain. The neuroinvasive nature of coronaviruses has been documented for different members of the betacoronaviruses such as SARS-CoV, MERS-CoV, HCoV-229E, HCoV-OC43, mouse hepatitis virus (MHV). Since coronaviruses use the cell surface receptor protein ACE-2, now the question arises do cells of the brain express the ACE-2 receptor? Well, the answer is not known clearly yet but mice transgenic (Tg) for the expression of human ACE-2 (hACE-2), called K18-hACE2 mice, showed extremely susceptible to the SARS-CoV with the infection of the lungs and brain in all the experimental mice which were infected with intranasal inoculation. Later it had been reported that SARS-CoV causes the neural death in the brain of K18-hACE2 mice even in the absence of encephalitis. There is another report to have SARS-CoV RNA polymerase gene in the neurons of the infected person indicating neurons might have the viral receptor ACE-2 but more studies are required to make sure the existence of SARS-CoV in the neurons.

Several other recent reports described COVID-19 patients experienced with anosmia and ageusia which might be due to an invasion of this virus into the brain causing olfactory and gustatory dysfunctions. In one study of 417 mild to moderate COVID-19 patients with the general symptoms like cough, myalgia and loss of appetite, about 85.6% and 88% of patients suffered from olfactory and gustatory dysfunctions, respectively. In another study of 72 COVID-19 patients in Italy, 60 cases had variable degree of hyposmia with 2 cases were anosmia and 33 cases had hypogeusia with 1 case was ageusia suggesting anosmia and ageusia as initial or unique symptoms after SARS-CoV-2 virus infection. Since neither the olfactory neuron nor the other brain cells express the surface receptor ACE-2 for viral entry, further research is urgently required to solve this issue of how the olfactory or gustatory related neurons are affected due to SARS-CoV-2 virus infection.

There is an alternative way of 2019-nCoV invasion into the brain of COVID-19 patient is described by Kabbani and Olds. According to them if brain is susceptible to 2019-nCoV infection then persons will be at high risk whose are with the habit of smoking. Functional interactions between nicotine exposure and ACE2 expression in lungs and other organ systems such as heart and kidneys, as well as nicotine and other components of the renin-angiotensin system (RAS) suggest that smoking can promote 2019-nCoV cellular entry through nicoitnic acetylcholine receptor (nAChR) signaling. Kabbani and Oldssuggest that regions, which are known to express various types of nAChRs, are putative sites for primary infection with COVID-19 in the human brain. Interactions between nAChRs and ACE2 have been studied in several of these regions including the ventrolateral medulla and smoking may lead to enhanced viral infection through the ability of nicotine to upregulate nAChRs in regions such as the lungs. In this case, upregulation of nAChRs in either/neither neurons and astrocytes could promote greater viral entry and replication through augmented ACE2 expression in the cell. Supporting the notion that smokers are at the high risk to be infected by SARS-CoV, there is another report which demonstrated that ACE-2 expressions are increased in the small airway epithelia of smokers. Dealing with all these, SARS-CoV might infect brain tissue where smokers are at high risk of it.

**CONCLUSION**

In conclusion, we may say COVID-19 patients might die due to lack of oxygen as lungs are suffering from ARDS. But as the infection progress within the body, various other organs are being affected. But it is not yet known, other organs are affected due to the direct attack of this virus or as a consequences of lack of oxygen since lungs are not working properly or any other unknown underlying reasons. More extensive research is required further to rule out these possibilities.

**ACKNOWLEDGMENTS**

We thank department of Biochemistry and Molecular Biology, Jahangirnagar University, for their effort to complete this study.
REFERENCES

1. Stephen NJK, Gert U, van Zyl, Louise N, Monique IA, Wolfgang P. Human coronaviruses. Virology, Churchill Livingstone; 2012.94 p.
2. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003; 348:1967-1976.
3. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1951-1966.
4. van der Hoek L, Pyrc K, Jehnkh MF, et al. Identification of a new human coronavirus. Nat Med 2004;10:368-373.
5. Wuu PC, Lai SK, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, HKU1, from patients with pneumonia. J Virol 2005;79:884-895.
6. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1851-1858.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients with infected with novel coronavirus in Wuhan, China. Lancet 2020;395:497-504.
8. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019.N Engl J Med 2020;382:727-733.
9. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed March 30, 2021).
10. Li H, Zhou Y, Zhang M, Wang H, Zhao Q, Liu J. Updated approaches against SARS-CoV-2. Antimicrob Agents Chemother 2020; 64:e00483-20.doi: 10.1128/AAC.00483-20.
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.
12. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA2020;323:1061-1069.
13. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105924.
14. Goh KJ, Choong MC, Cheong EH, et al. Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from COVID-19 Infection. Ann Acad Med Singapore 2020;49:108-118.
15. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-273.
16. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631-637.
17. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002;532:107-110.
18. Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin I-9. Circ Res2000;87:E1-9.
19. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-1263.
20. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514-523.
21. Pan F, Ye T, Sun P, et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. Radiology 2020;295:715-721.
22. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. EurRespir J 2020;55:2000607.
23. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-280.
24. Tang NL, Chan PK, Wong CK, et al. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. ClinChem 2005;51:2333-2340.
25. Mossel EC, Wang J, Jeffers S, et al. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. Virology 2008;372:127-135.
26. Weinheimeir VK, Becher A, Tonnies M, et al. Influenza A viruses target type II pneumocytes in the human lung. J Infect Dis 2012;206:1685-1694.
27. Mason RJ. Biology of alveolar type II cells.Respirology 2006;Suppl:S12-5.
28. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. SeminImmunopathol 2017;39:517-528.
29. Renghunathan R, Jayapal M, Hsu LY, et al. Expression profile of immune response genes in patients with Severe Acute Respiratory Syndrome. BMC Immunol 2005;6:2.
30. Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). Virus Res 2008;133:13-9.
31. Herold S, Steinmueller M, von Wulffen W, et al. Lung epithelial apoptosis in influenza virus pneumonia: the role of macrophage-expressed TNF-related apoptosis-inducing ligand. J Exp Med 2008;205:3065-3077.
32. Högnér K, Wolff T, Pleschka S, et al. Macrophage-expressed IFN-β Contributes to Apoptotic Alveolar Epithelial Cell Injury in Severe Influenza Virus Pneumonia. PLoSPathog 2016;12:e1005716.
33. Pan L, Mu M, Yang P, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol 2020;115:766-773.
34. D’Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. ClinGastroenterolHepatol 2020;18:1663-1672.
35. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor. Cell2020;181:271-280.
36. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol 2020;94: e00127-20.
37. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020;158:1519.
38. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002;532:107-110.
39. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579:265-269.
40. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-574.
41. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology 2020;158:1518-1519.
42. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. ClinChem Lab Med 2020;58:1116-1120.
43. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost 2020;18:844-847.
44. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020;18:1094-1099.
45. Akhmerov A, Marban E. COVID-19 and the Heart. Circ Res 2020;126:1443-1455.
46. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323:1612-1614.
47. Raan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-848.
48. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.
49. Tiganelli CJ, Ingraham, Sparks MA, et al. Antihypertensive drugs and risk of COVID-19? Lancet Respir Med 2020;8:e30-e31.
50. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720.
51. Izedine H, Jhaeveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. Kidney Int 2020;97:1297-1298.
52. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829-838.
53. Guan GW, Gao L, Wang JW, et al. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. ZhonghuaGanZangZhi Bing ZaZhi 2020;28:100-106.
54. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol 2020;73:566-574.
55. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.
56. Bangash MN, Patel J, Parakh D. COVID-19 and the liver: little cause for concern. Lancet GastroenterolHepatol 2020;5:529-530.
57. Michalovich A, Bhide K, Bhide M, Kováč A. How viruses infiltrate the central nervous system. ActaVirol 2017;61:393-400.
58. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. J Immunol 2004;173:4030-4039.
59. Li K, Wohlford-Lenane C, Perlm S, et al. Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4. J Infect Dis 2016;213:712-722.
60. Talbot PJ, Ekandé S, Cashman NR, Mounir S, Stewart JN. Neurotropism of human coronavirus 229E. AdvExp Med Biol 1993;342:339-346.
61. Dubé M, Le Coupene A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43.J Virol 2018;92:e00404-18.
62. Zhou X, Huang F, Xu L, et al. Hepatitis E Virus Infects Neurons and Brains. J Infect Dis2017;215:1197-1206.
63. McCray PB Jr, Pewe L, Wohlford-Lenane C, et al. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J Virol 2007;81:813-821.
64. Netland J, Meyerholz DK, Moore S, Cassell M, Perlm S. Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. J Virol 2008;82:7264-7275.
65. Zhang QL, Ding YQ, Hou Jl, et al. Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with in situ hybridization. Di Yi Jun Yi Da XueXueBao 2003;23:1125-1127.
66. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277:2251-2261.
67. Moein ST, Hashemian SMR, Mansourafshar B, Khorraram- Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID- 19. Int Forum Allergy Rhinol 2020;10:944-950.
68. Lee Y, Min P, Lee S, Kim SW. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. J Korean Med Sci 2020; 35: e174.
69. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: a single-center experience on 72 cases. Head Neck 2020;42:1252-1258.
70. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. Mol Pharmacol 2020;97: 351-353.
71. Leung JM, Yang CX, Tam A, et al. ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. EurRespir J 2020;55:2000688.