WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 4, 1865-1884. Review Article ISSN 2277– 7105

MECHANISM OF COVID-19 INDUCED RESPIRATORY FAILURE, IT'S EFFECTS ON OTHER ORGAN SYSTEMS IN HUMANS

G. Nagendra Babu[1], Bhanu Pratap Singh*[2], Aditya Anand[3] and Shubhankar Anand[4]

[1]Department of Pharmaceutical Engineering and Technology, IIT (BHU), Varanasi.

[2,3,4]School of Biochemical Engineering, IIT (BHU), Varanasi.

Article Received on
20 Feb. 2021,

Revised on 12 March 2021,
Accepted on 01 April 2021

DOI: 10.20959/wjpr20214-20236

***Corresponding Author**
Bhanu Pratap Singh
School of Biochemical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi.

ABSTRACT

COVIDS are a group of encompassed infections with positive sense, non fragmented, single abandoned RNA genomes. The subgroups of COVID family are alpha (α), beta (β), gamma (γ) and delta (δ) COVID. The ICTV named the infection as SARS-CoV-2, a gathering of virologists in China proposed renaming SARS-CoV-2 as human COVID 2019 (HCoV-19), taking into account that such a name would perceive the infection from SARS-CoV and keep it consistent with the WHO name of the malady it causes, Coronavirus. SARS-CoV-2 was accounted for to be an individual from the β gathering of COVIDs. All out six HCoVs are recognized in particular HCoV-229E, NL63, OC43, HKU1, SARS-CoV and MERS-CoV. But SARS-CoV AND MERS-CoV other output cause dangerous pneumonia and bronchiolitis particularly in old, kids and immunocompromised patients by acting on lungs. Apart from, these additionally act on several other organ systems i.e. heart, GI, liver, and brain which cause exacerbation of infections related to particular organ system and exacerbate the disease condition. In this study we focusing on the mechanism by which SARS-CoV causes the respiratory failure and its effect on several other organ systems of human.

KEYWORDS: SARS-CoV, organ systems, respiratory failure.

1. INTRODUCTION

Novel Coronavirus-induced pneumonia was identified on 11 February 2020 by the WHO as coronavirus disease 2019 (COVID-19). It has increased rapidly in epidemic scale it first emerged in December 2019 in Wuhan, China(Li et al., 2020b, Zhou et al., 2020). Almost at the same day, the International Commission for the Classification of Viruses announced that

the novel coronavirus was termed as severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 is not the first serious outbreak of acute respiratory disease induced by coronavirus, the coronavirus has led three epidemic diseases within a short period of time (since the last two decades to so far), the first is recognized as severe acute respirator syndrome (SARS) and the second is regarded as middle-eastern respiratory syndrome (MERS)(de Wit et al., 2016) and finally the third is coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)(Wu et al., 2020b, Li et al., 2020b). It presents clinical symptoms such as fever, non-productive cough, dyspnea, myalgia, fatigue, reduced leukocyte counts and radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and MERS-CoV infections(Wu et al., 2020a, Li et al., 2020b). Currently COVID-19 cases have been found in many countries across the globe. According to the latest statistics, the number of confirmed cases in China reached 79,968 by March 1, 2020, of which 2,873 were dead, and 41,681 have been cured. Besides China, the number of confirmed cases in other countries also reached 7,041, of which 105 were dead, and 459 were cured. On 31 January 2020, the World Health Organization (WHO) reported that COVID-19 was considered as an international public health emergency (PHEIC), which means it may pose an immediate threat to several countries and needs an unified international response(Li et al., 2020b). Hence, as soon as possible currently we need to develop the appropriate pharmaceutical products for COVID-19 therapy. Therefore, this study is focuses on the mechanism contributing to the COVID-19 patho-physiology that leads to respiratory failure and also effect on other organs including brain.

2. Mechanism of COVID-19 induced respiratory failure

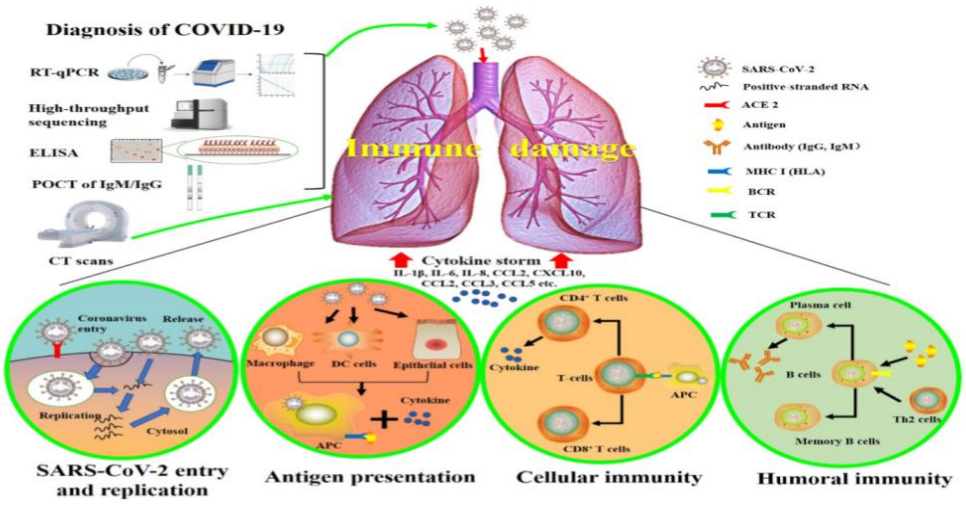

Figure 1: Detailed mechanism of COVID-19 (Li et al., 2003b, Hoffmann et al., 2020).

2.1 SARS-CoV-2 entry and replication

Coronavirus spike (S) protein enables viral penetration into target cells. Entry is based on binding the surface component, S1, of the S protein to a cellular receptor that facilitates viral attachment to the target cell surface. Furthermore, entry requires S protein priming by cellular proteases, which includes S protein cleavage at the site of S1/S2 and S2 and enables viral and cell membrane fusion, a process driven by the S2 subunit (**Figure 1**).SARS-S requires angiotensin-converting enzyme 2 (ACE2)(Li et al., 2003b, Hoffmann et al., 2020) as an entry receptor and utilizes TMPRSS2 cell serine protease for S protein priming(Glowacka et al., 2011, Hoffmann et al., 2020). At the atomic level, the SARS-S/ACE2 interface was explored, and the productivity of use of ACE2 was found to be a primary determinant of SARS-CoV transmissibility(Li et al., 2005, Hoffmann et al., 2020). Latest studies have shown that SARS-S and SARS-2-S share an origin of around 76% of amino acids. It has also been found that SARS-2-S also employs ACE2 and TMPRSS2 for entry of host cells just like SARS-S.

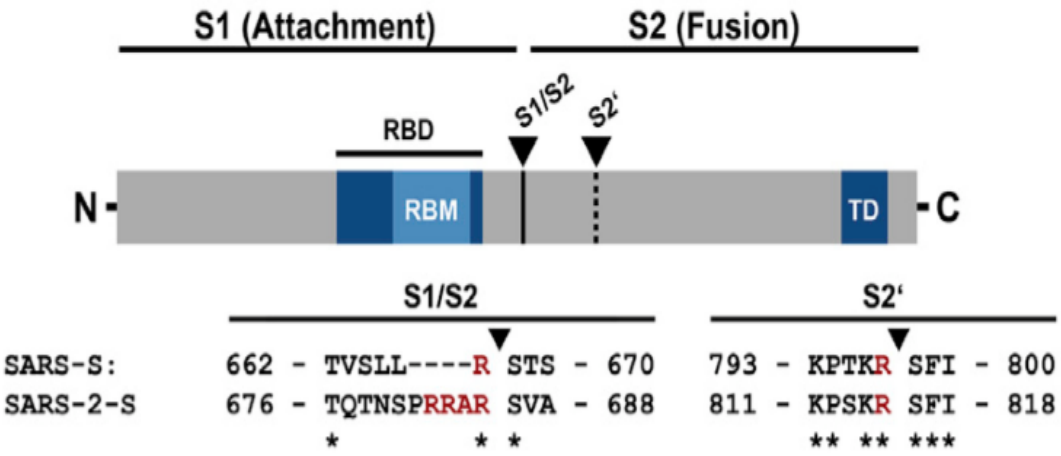

Figure 2: SARS-S schematic diagram including functional domains (RBD, binding receptor domain; RBM, binding receptor motif; TD, trans membrane domain) and proteolytic cleavage sites (S1/S2, S20); Sequences of amino acids around the two (red) protease recognition sites are shown for SARS-S and SARS-2-S (asterisks indicate conserved residues). Arrow heads signify the place of cleavage. (Hofmann et al., 2004, Glowacka et al., 2011, Hoffmann et al., 2020).

Proteolytic processing of SARS-2-S

SARS-2-S has been expressed using a high transfectability cell line, 293 T, and the proteolytic processing of the S protein was analysed because other coronavirus S proteins are cleaved in infected cells by host cell proteases at the S1/S2 cleavage site (**Figure 2**).

Immunoblot analysis of 293 T cells with a C-terminal antigenic tag expressing SARS-2-S protein showed a band with a molecular weight required for unprocessed S protein (S0). In cells and, more specifically, in SARS-2-S-bearing particles of vesicular stomatitis virus. In addition, as previously reported **(Hofmann et al., 2004, Glowacka et al., 2011, Hoffmann et al., 2020)**, an S2 signal was largely absent in the cells and particles expressing SARS-S. Such findings indicate an successful proteolytic processing of SARS-2-S in human cells, in line with the discovery of many arginine residues at the S1/S2 cleavage site of SARS-2-S but not SARS-S **(Figure 2).** In comparison, SARS-2-S' cleavage site was similar to SARS-S's.

SARS-2-S and SARS-S similarity in entry into cell line

Replication-defective coronavirus-S protein-bearing VSV particles diligently depict key aspects of coronavirus host cell entry (Kleine-Weber et al., 2019, Hoffmann et al., 2020). In this employed SARS-2-S-bearing VSV pseudotypes to test SARS-CoV-2 cell entry. Both SARS-2-S and SARS-S were robustly incorporated into VSV particles, allowing for a functional side-by-side comparison; however, comparable particle integration of the S1 subunit remains to be formally demonstrated. And also which cell lines were susceptible to SARS-2-S-driven entry, using a panel of well-defined lines of human and animal cells, respectively. As expected, all cell lines were readily susceptible to entry, guided by the pantropic VSV glycoprotein (VSV-G). Most of the human cell lines and the Vero and Madin-darby canine kidney 2 (MDCKII) animal cell lines were also susceptible to SARS-S induced entry. In addition, SARS-2-S allowed entry into an equivalent range of cell lines to SARS-S, indicating similarities in entry receptor selection.

SARS-CoV-2 Employs the SARS-CoV Receptor for Host Cell Entry

To explicate why SARS-S and SARS-2-S mediated entry into the same cell lines, researchers resolved next whether SARS-2-S harbors amino acid residues necessary for interaction with the SARS-S entry receptor ACE2. Sequence analysis showed that SARS-CoV-2 clusters with bats-related SARS-CoV viruses (SARSr-CoV), some of which can use ACE2 for host cell entry, but not all. Analysis of the receptor binding motif (RBM), a portion of the receptor binding domain (RBD) that interacts with ACE2, confirmed that most of the amino acid residues important to SARS-S binding with ACE2 were conserved in SARS-2-S(Ge et al., 2013, Hoffmann et al., 2020). In compliance with these observations, direct human and bat (Rhinolophus alcyone)expression of ACE2 but not human dipeptidyl peptidase-4 (DPP4), the entry receptor used by MERS-CoV(Raj et al., 2013, Hoffmann et al., 2020), or human

alanine aminopeptidase N(APN), the entry receptor used by HCoV-229E(Yeager et al., 1992, Hoffmann et al., 2020), and allowed entry into non-susceptible baby hamster kidney (BHK-21) cells by SARS-2-S- and SARS-S-driven means. In addition, antiserum elevated against human ACE2 blocked entry powered by SARS-S- and SARS-2-S-but not by VSV-G- or MERS-S. Eventually, authentic BHK-21 cells infected with SARS-CoV-2 are transfected to express ACE2 cells but not high-efficiency parental BHK-21 cells, suggesting that SARS-2-S, uses ACE2 for cell entry as like SARS-S (**Figure 3**).

The Cellular Serine Protease TMPRSS2 Primes SARS-2-S for Entry, and a Serine Protease Inhibitor Blocks SARS-CoV-2 Infection of Lung Cells

In this examined the SARS-CoV-2 entry protease dependency. SARS-CoV can use the endosomal cysteine proteases cathepsin B and L (CatB / L)(Simmons et al., 2005, Hoffmann et al., 2020) and serine protease TMPRSS2 for S protein priming in cell lines(Glowacka et al., 2011), and both proteases need to be inhibited for robust viral entry blockage(Kawase et al., 2012). Nevertheless, only TMPRSS2 activity is necessary in the infected host for viral dissemination and pathogenesis, while CatB / L activity is expendable(Iwata-Yoshikawa et al., 2019, Hoffmann et al., 2020).

To decide whether SARS-CoV-2 can use CatB / L for cell entry, initially used ammonium chloride, which elevates endosomal pH and thus blocks CatB /L activity. Targets included 293 T cells (TMPRSS2-, transfected to express ACE2 for robust S protein-driven entry) and Caco-2 cells (TMPRSS2+). Ammonium chloride blocked VSV-G-dependent entry into both cell lines while Nipah-driven F and G-protein entry was not affected, which was consistent with Nipah virus but not VSV being able to fuse directly with the plasma membrane(Bossart et al., 2002, Hoffmann et al., 2020). Treatment with ammonium chloride strongly inhibited SARS-2-S- and SARS-S-driven entry into TMPRSS2-293 T cells, indicating dependence on CatB / L. Inhibition of entry into TMPRSS2 + Caco-2 cells was less effective compared with 293 T cells, which in Caco-2 cells would be consistent with SARS-2-S priming by TMPRSS2.Furthermore, SARS-2-S-driven entry into Caco-2 and Vero-TMPRSS2 cells was partially blocked by the clinically validated serine protease inhibitor Camostat mesylate that is active against TMPRSS2(Kawase et al., 2012, Hoffmann et al., 2020), Total inhibition was achieved with the use of Camostat mesylate and CatB / L inhibitor E-64d, suggesting that both CatB / L and TMPRSS2 can be used by SARS-2-S for priming in these cell lineages. Camostat mesylate, on the other hand, did not interfere with SARS-2-S-driven entry into the

293 T and Vero TMPRSS2 cell lines, which was effectively blocked by E-64d and thus dependent on CatB / L.In addition, TMPRSS2 regulated expression retrieved SARS-2S-driven entry from E-64d inhibition, confirming that SARS-2-S can utilize TMPRSS2 for S protein priming. Then later examined whether use of TMPRSS2 is appropriate for infection with SARS-CoV-2 lung cells. Nonetheless, Camostat mesylate significantly lowered the entry of MERS-S-, SARS-S-, and SARS-2-S- into the lung cell line Calu-3 but not VSV-G-driven and did not exert any unwanted cytotoxic impact. Similarly, treatment with Camostat mesylate greatly reduced an authentic SARS-CoV-2 infection with Calu-3.Eventually, SARS-S and SARS-2-S- but not VSV-G-driven entry into primary human lung cells is prevented by the treatment with Camostat mesylate. Finally TMPRSS2 may be used selectively by SARS-CoV-2 for S protein priming and Camostat mesylate, and a TMPRSS2 inhibitor, which prevents SARS-CoV-2 lung cell infection(Hoffmann et al., 2020).antibody responses elevated against SARS-S that provide some degree of protection against SARS-CoV-2(Hoffmann et al., 2020).

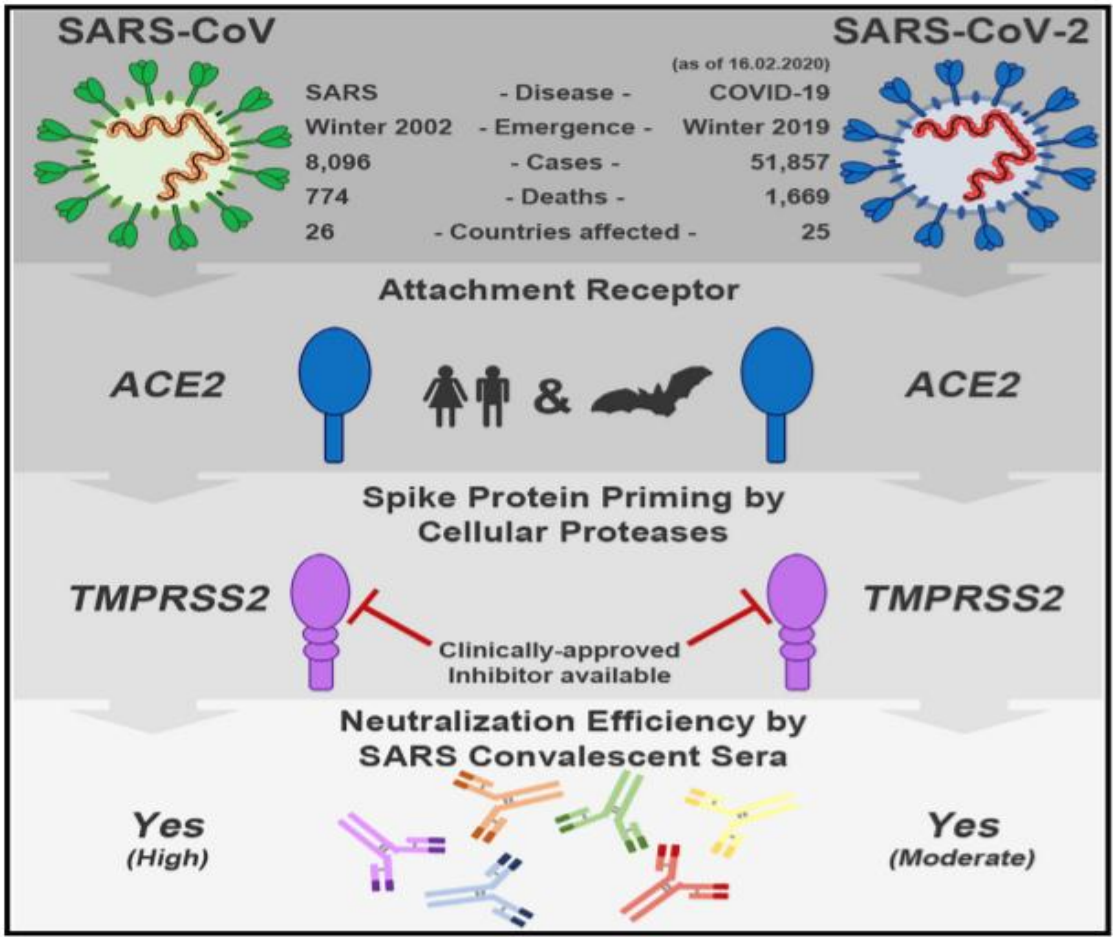

Figure 3: Similarities between SARS-CoV-2 and SARS-CoV (Yeager et al., 1992, Hoffmann et al., 2020).

2.2 Antigen presentation

When the virus reaches the cells, it must deliver its antigen to the antigen presentation cells (APC), which is a key part of the body's anti-viral immune system. Major histocompatibility complex or humans leukocyte antigen (MHC or HLA) in humans produces antigenic peptides and is then recognized by virus-specific cytotoxic T lymphocytes (CTLs). Therefore the interpretation of SARS-CoV-2 antigen presentation will aid further interpretation of COVID-19 pathogenesis. Regrettably, currently there are no reports on this, but we can get some knowledge from prior SARS-CoV so MERS-CoV studies. SARS-CoV's antigen presentation relies mainly on MHC I(Liu et al., 2010, Li et al., 2020b) molecules but MHC II also contributes to its presentation. Previous work shows various HLA polymorphisms that are associated with SARS-CoV susceptibility. In addition, the gene polymorphisms associated with antigen presentation of MBL (mannose-binding lectin) are linked to the risk of SARS-CoV infection. Working on these we can get beneficial knowledge on pathogenesis of COVID-19 and diagnosis, treatment strategies(Li et al., 2020b).

2.3 Humoral and cellular immunity

Subsequently, antigen presentation activates the humoral and cellular immunity of the body, which is mediated by B and Tcells unique to the viruses. Compared to typical acute viral infections, the antibody profile against SARS-CoV virus has a characteristic pattern of producing IgM and IgG. After some time the SARS-specific IgM antibodies vanish while the IgG antibody will last for a long time, which suggests that IgG antibodies will play a defensive role(Li et al., 2003a, Li et al., 2020b), and the SARS-specific IgG antibodies are mainly S-specific and N-specific antibodies. There are more work on the cellular immunity of coronavirus relative to humoral responses. One of the study indicates that the amount of CD4+ and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients is substantially reduced(Xu et al.). Likewise, in patients with SARS-CoV, the acute phase response is associated with a significant decrease inCD4+ and CD8+ T-cells. A similar impact on MERS-CoV clearance in mice expressed in the particular CD8+ T cells. These conclusions may provide useful information for the development of appropriate SARS-CoV-2 vaccines(Li et al., 2020b).

2.4 Cytokine storm

The literature indicates that acute respiratory distress syndrome (ARDS) is COVID-19's principal cause of death. Six of the 41 patients admitted to SARS-CoV-2 during the early

stages of the outbreak died from ARDS(Huang, 2019, Li et al., 2020b). ARDS is the common immune-pathological phenomenon in infections with SARS-CoV-2, SARS-CoV, and MERS-CoV. One of the key mechanisms for ARDS is the cytokine wind, After the SARS-CoV-2 infection, pathogenic T cells are rapidly activated, producing granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6 and other pro- inflammatory factors (**Figure 4**). GM-CSF will further activate CD14+CD16+ inflammatory monocytes, producing a larger amount of IL-6 and other pro inflammatory factors (Huang 2019, Feng, Zheng et al. 2020, Li, Geng et al. 2020). , and thereby inducing an inflammatory "storm" that leads to immune damage, ARDS and damage other organs, such as the lungs and the liver. Eventually lead to death in extreme cases of SARS-CoV2 infection, just as it does in SARS-CoV and MERS-CoV infections.

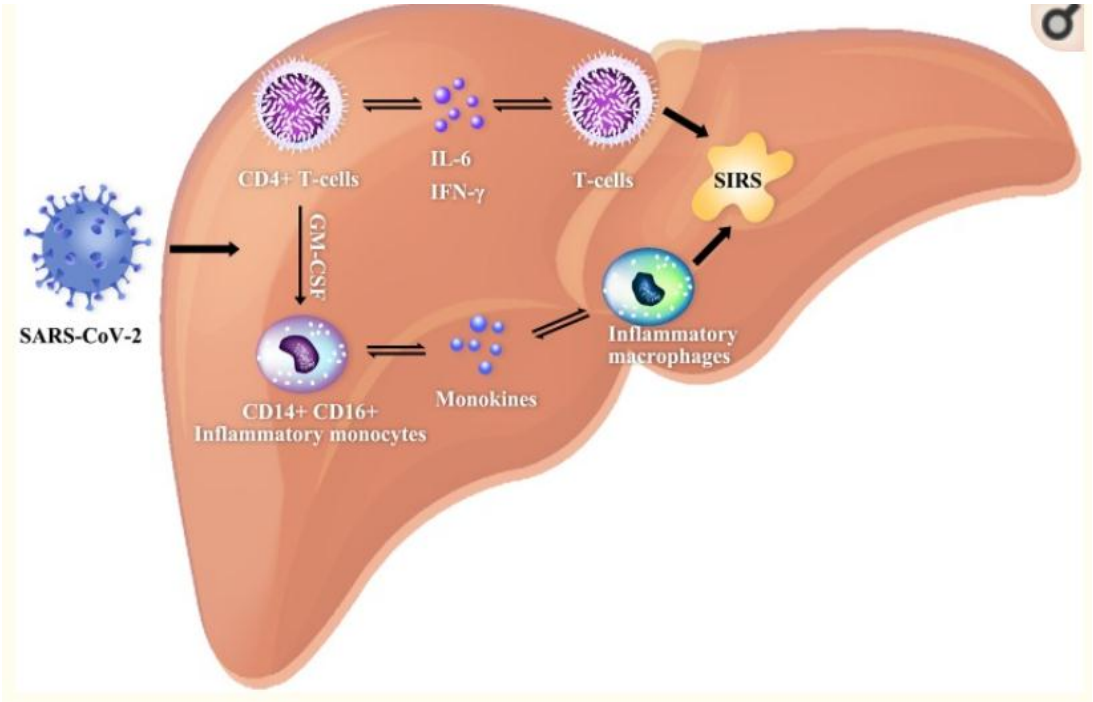

Figure 4: Schematic diagram showing the systemic inflammatory response induced by SARS-CoV2. (Huang 2019, Feng, Zheng et al. 2020, Li, Geng et al. 2020)

2.5 Immune evasion

SARS-CoV and MERS-CoV use several methods to suppress immune responses in order to better exist in host cells. The pattern recognition receptors (PRRs) can recognize the evolutionarily retained microbial structures called pathogen-associated molecular patterns (PAMPs). SARS-CoV and MERS-CoV, however, may induce the formation of double-membrane vesicles that lack PRRs and then multiply in these vesicles by avoiding their

dsRNA(Heath et al., 2006, Li et al., 2020b) host detection. IFN-I(IFN-a and IFN-b) have a protective effect on infection with SARS-CoV and MERS-CoV but IFN-I is inhibited in infected mice.MERSCoV's Accessory Protein 4a can block IFN induction at MDA5 activation level by direct contact with double-stranded RNA. In addition ORF4a, ORF4b, ORF5, and MERSCoV membrane proteins inhibit IFN regulatory factor 3 (IRF3) nuclear transport and IFNb promoter activation. Coronavirus may also affect the antigen present at ion. For example, after a MERS-CoV infection, gene expression associated with antigen presentation is down-regulated(Menachery et al., 2018, Li et al., 2020b). Hence The elimination of the immune evasion of SARSCoV-2 was crucial in its treatment and in the production of peculiar drugs.

3. COVID-19 on other organ systems

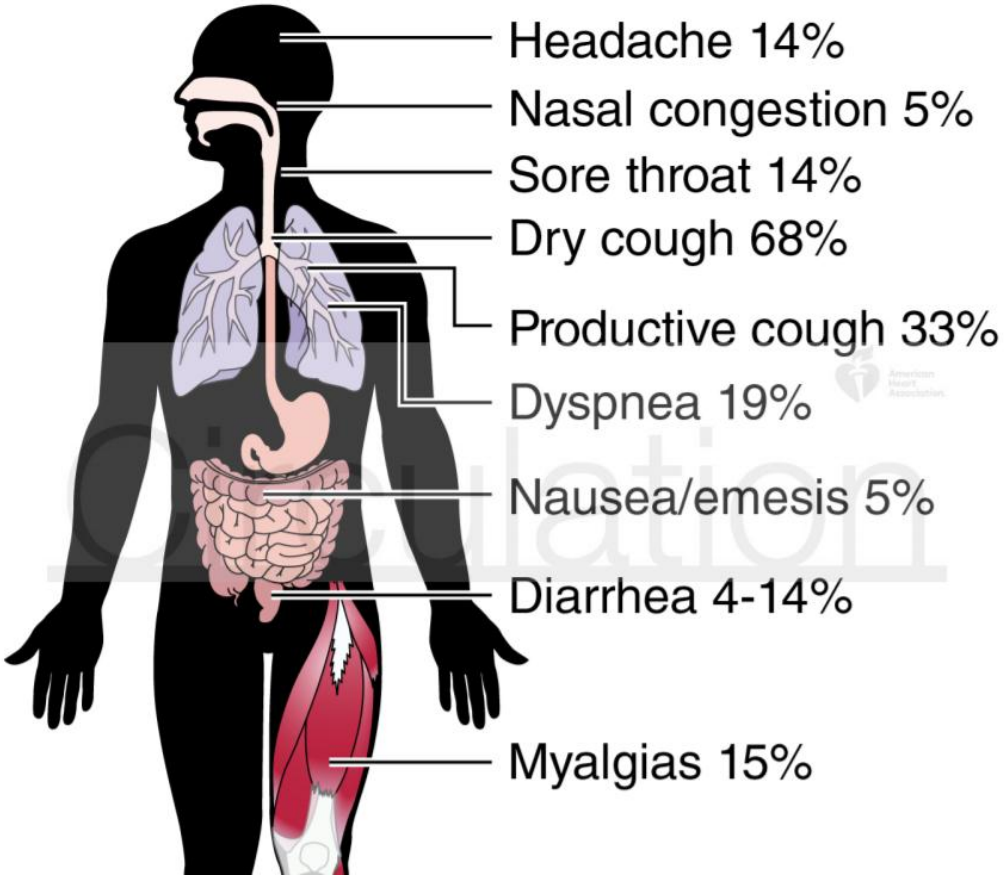

Figure 5: Effects of COVID- 19 on organ systems (American Heart Association).

3.1 Cardiovascular system

SARS- CoV-2 and ACE2

Angiotensin-converting enzyme 2 (ACE2) is an aminopeptidase bound to the membrane that plays a critical role in cardiovascular and immune systems. ACE2 is involved in heart

function and in the creation of hypertension and mellitus diabetes mellitus. Consequently, ACE2 has been recognized as a functional coronavirus receptor like SARS-CoV and SARS-CoV-2. SARS- Infection with CoV-2 is caused by binding the virus spike protein to ACE2, which is strongly expressed in the heart and lungs(Turner et al., 2004, Zheng et al., 2020). SARS-CoV-2 primarily invades alveolar epithelial cells, causing symptoms of the respiratory tract. These symptoms are more severe in CVD patients, which may be associated with increased ACE2 secretion in these patients as opposed to healthy individuals. The use of renin-angiotensin-aldosterone system inhibitors will increase the ACE2 levels. Since ACE2 is a functional receptor for SARS-CoV-2, the safety and potential consequences of anti-hypertension therapy with ACE inhibitors or angiotensin-receptor blockers should be carefully considered in COVID-19 patients.

Acute cardiac injury

previous studies indicated that coronavirus-related Middle East respiratory syndrome (MERS- CoV) can cause acute myocarditis and heart failure(Alhogbani, 2016, Zheng et al., 2020). SARS- CoV-2 and MERS- CoV are equally pathogenic and the myocardial damage caused by infection with these viruses certainly increases the patient's complexity. In 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, myocardial injury associated with SARS-CoV-2 occurred, primarily as an rise in cardiac troponin I (hs-cTnI) levels of high sensitivity (> 28 pg / ml)(Huang et al., 2020, Zheng et al., 2020). And also four of five patients with myocardial injury were admitted to the intensive- care unit (ICU), which indicates the serious nature of the myocardial injury in patients with COVID-19.

Similarly, among confirmed cases of SARS-CoV-2 infection identified by China's National Health Commission (NHC), some of the patients first went to see a doctor due to cardiovascular symptoms. The patients showed palpitations of the heart and tightness of the chest rather than respiratory symptoms such as fever and cough, and were later diagnosed with COVID-19. For those identified by the NHC who died from COVID-19, 11.8 percent of patients without underlying CVD had significant heart damage, with elevated rates of cTnI or cardiac arrest during hospitalization. Hence the frequency of cardiovascular symptoms is high in patients with COVID-19 due to systemic inflammatory response and defects of the immune system during disease progression. The mechanism of the acute myocardial injury caused by infection with SARS-CoV-2 could be linked to ACE2.ACE2 is commonly expressed not only in the lungs but also in the cardiovascular system and, thus, the signaling

mechanisms associated with ACE2 can also play a role in heart injury. Other possible mechanisms of myocardial injury include a cytokine storm caused by an imbalanced response by Type 1 and Type 2 T helper cells(Huang et al., 2020, Zheng et al., 2020) and COVID-19-induced respiratory dysfunction and hypoxaemia resulting in myocardial cell damage.

Chronic cardiovascular damage

A 12-year study of 25 patients suffering from SARS-CoV infection showed that 68% had hyperlipidaemia, 44% had cardiovascular system defects and 60% had glucose metabolism disorders(Wu et al., 2017, Zheng et al., 2020). Study of metabolomics has shown dysregulation of lipid metabolism in patients with a history of SARS-CoV infection. The serum concentrations of free fatty acids, lysophosphatidylcholine, lysophosphatidylethanola-mine and phosphatidylglycerol in these patients were substantially increased relative to those without a history of SARS-CoV infection(Wu et al., 2017).Nevertheless, the mechanisms by which infection with SARS-CoV contributes to lipid and glucose metabolism disorders are still unclear. Since SARS-CoV-2 has a similar structure to SARS-CoV, this novel virus may also cause chronic cardiovascular system damage, and attention should be paid to cardiovascular safety during COVID-19 treatment(Zheng et al., 2020).

Patients with pre-existing CVD

A meta-analysis found that in patients with underlying CVD, MERS-CoV infection was more likely to occur(Badawi and Ryoo, 2016, Zheng et al., 2020). 50 percent had hypertension and diabetes and up to 30 percent had heart disease in patients with MERS-CoV infection and serious symptoms. Likewise, based on the current New Coronavirus Infection Pneumonitis Diagnosis and Treatment Program (Trial Version 4), older people with comorbidity are more likely to become infected with SARS-CoV-2, particularly those with hypertension, coronary heart disease or diabetes. However, when diagnosed with SARS-CoV-2, patients with CVD are more likely to experience serious symptoms. Hence patients with CVD account for a substantial proportion of COVID-19 deaths.

3.2 Gastro-Intestinal system

According to evidence from earlier SARS research, the gastrointestinal tract (intestine) tropism of SARS coronavirus (SARS-CoV) has been confirmed by viral recognition in biopsy samples and stools including in discharged patients, which could provide partial hypotheses for gastrointestinal symptoms, conceivable reoccurrence, and dissemination of SARS from stubbornly shedding humans(Leung et al., 2003, Gu et al., 2020). More recently,

2 independent laboratories in China have announced that they have successfully isolated live 2019-nCoV (unpublished) from patient stools. Taken collectively, an many number of clinical evidence tells us that digestive systems other than respiratory systems can serve as an alternative path of infection when people are in contact with infected wildlife or sufferers, and symptomless carriers or individuals with mild enteric symptoms.

Medical professionals should be vigilant to classify patients with initial gastrointestinal symptoms immediately, and evaluate the length of the infection with delayed viral conversion. Up to now, molecular modelling has revealed through the next-generation sequencing technology that 2019nCoV shares approximately 79% of the sequence associated with SARS-CoV, indicative of these 2 lineage B β-coronaviruses highly homologous, and angiotensin converting enzyme II (ACE2), previously known as SARS-CoV entry receptor, was confirmed solely in 2019-nCoV infection amid amino acid mutations at some essential receptor binding domains(Lu et al., 2020, Gu et al., 2020).It is universally accepted that coronavirus human transmissibility and pathogenesis rely primarily on its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS), with binding affinity of 2019-nCoV(Gu et al., 2020), including virus attachment, receptor recognition, protease cleaving, and membrane fusion.

Latest bioinformatics analyzes of available single-cell transcriptom data from normal human lung and gastrointestinal system were conducted to classify the ACE2-expressing cell distribution and percentage, and revealed that ACE2 was hugely expressed not only in lung AT2 cells, but also in upper and stratified epithelial oesophagus and Ileum and colon absorptive enterocytes**(Figure 6)**(Zhang et al., 2020, Gu et al., 2020).With the increasing permeability of the gastrointestinal wall to foreign pathogens once infected with the virus, enteric symptoms such as diarrhoea would occur via malabsorption of invaded enterocytes, which in principle suggested that the digestive system may be susceptible to COVID-19. By comparison, since ACE2 and TMPRSS in particular TMPRSS2 are co-located in the same host cells and the latter exert hydrolytic effects responsible for S-protein priming and viral entry into target cells, subsequent bioinformatics studies provide additional evidence of COVID-19 enteric infectivity in that the high co-expression ratio was observed in absorptive enterocytes and upper epithelial cells of oesophagus besides lung AT2 cells. Nevertheless, the precise cause of the gastrointestinal symptoms caused by COVID-19 remains unclear. ACE2-

related COVID-19 approaches such as ACE2 fusion proteins and TMPRSS2 inhibitors can aid in the treatment of COVD-19.

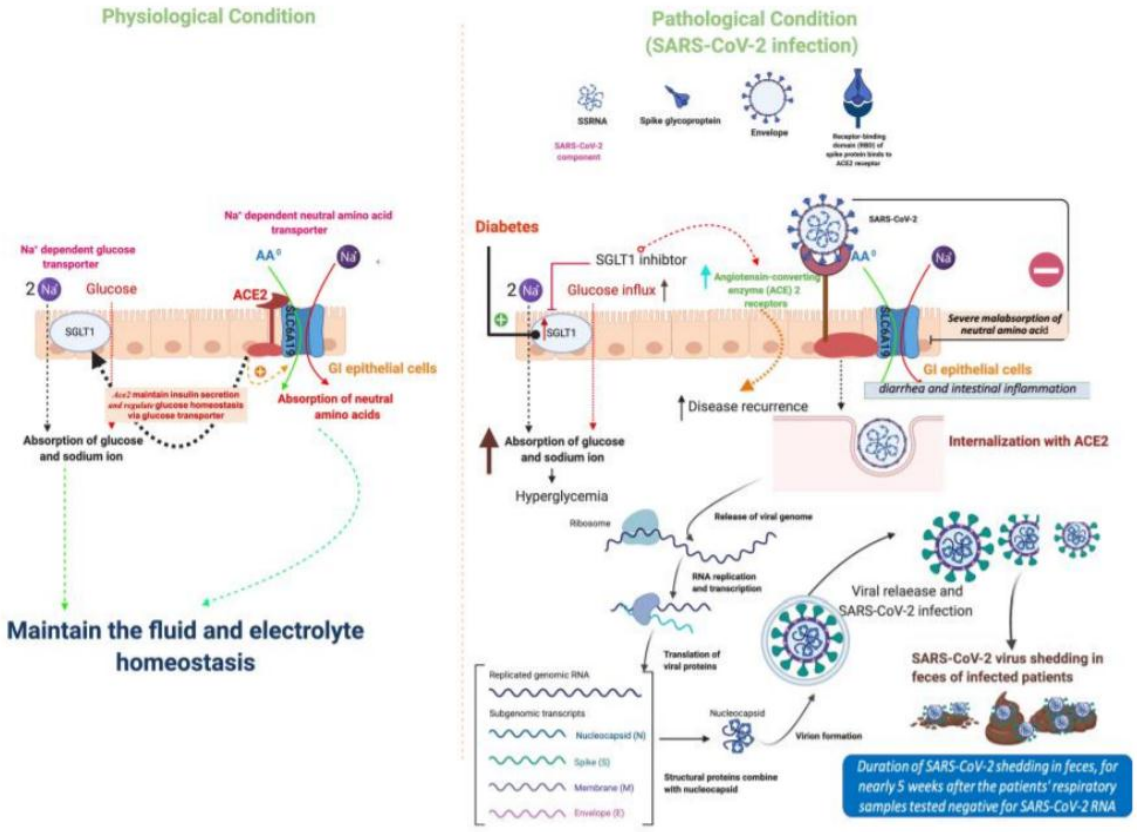

Figure 6: Interaction of SARS-CoV-2 with ACE-2 of GI epithelial cells (Zhang et al., 2020, Gu et al., 2020).

3.3 Liver

Several studies have indicated that SARS-CoV-2 primarily reaches alveolar epithelial cells via the human ACE2 receptor(Li et al., 2020a, Feng et al., 2020). Hence the lung is known to be the key target organ of SARS-CoV-2 infection. Nonetheless, previous studies have shown that bile duct epithelial cells may also express ACE2 receptor at a level 20 times higher than in hepatocytes and these findings indicate that SARS-CoV-2 infection may also cause epithelial cell damage to the bile ducts(Chai et al., 2020, Feng et al., 2020)**.**However, substantial changes in circulating levels of serum alkaline phosphatase, bilirubin, or gamma-glutamyltransferase (which may indicate bile duct injury) were rarely recorded in COVID-19 patients(Guan et al., 2020, Feng et al., 2020). Liver histopathologic characteristics in COVID-19 patients also showed no significant damage to hepatocytes or bile duct cells(Xu et al., 2020, Feng et al., 2020)**.** It is therefore rational to conclude that COVID-19-related liver

dysfunction is more likely to result from secondary liver damage than the use of hepatotoxic therapies or the coexistence of systemic inflammatory response **(Figure 4**), hypoxia-induced respiratory distress syndrome, or multiple organ dysfunctions.

3.4 Brain

The transmission of COVID-19 in the systemic circulation or through the ethmoid bone cribriform plateclose to the olfactory bulb may lead to cerebral involvement, has already been confirmed in the past for patients affected by SARS-CoV(Netland et al., 2008, Baig et al., 2020). The presence of the COVID-19 virus in the circulation, it obviously migrates into the cerebral circulation. While slow blood flow inside the microcirculation may be one of the factors that may promote the interaction of the spike protein COVID-19 virus with ACE2expressed in capillary endothelium. Consequent budding of the capillary endothelium virus particles and damage to the endothelial lining may facilitate viral entrance to the brain. When in the neuronal tissue milieu, its interference with ACE2 receptors(**Figure 7**) expressed in neurons(Baig et al., 2020, Palasca et al., 2018) that induce a cascade of viral budding followed by neuronal damage without significant inflammation, as shown in previous cases of SARS-CoV(Netland et al., 2008, Baig et al., 2020).It is worth noting here that the endothelial ruptures in cerebral capillaries followed by bleeding inside the cerebral tissue may have lethal consequences in patients with COVID-19 infections.Furthermore, the observations such as an impaired ability to smell or hyposmia has been also found in COVID-19patient.

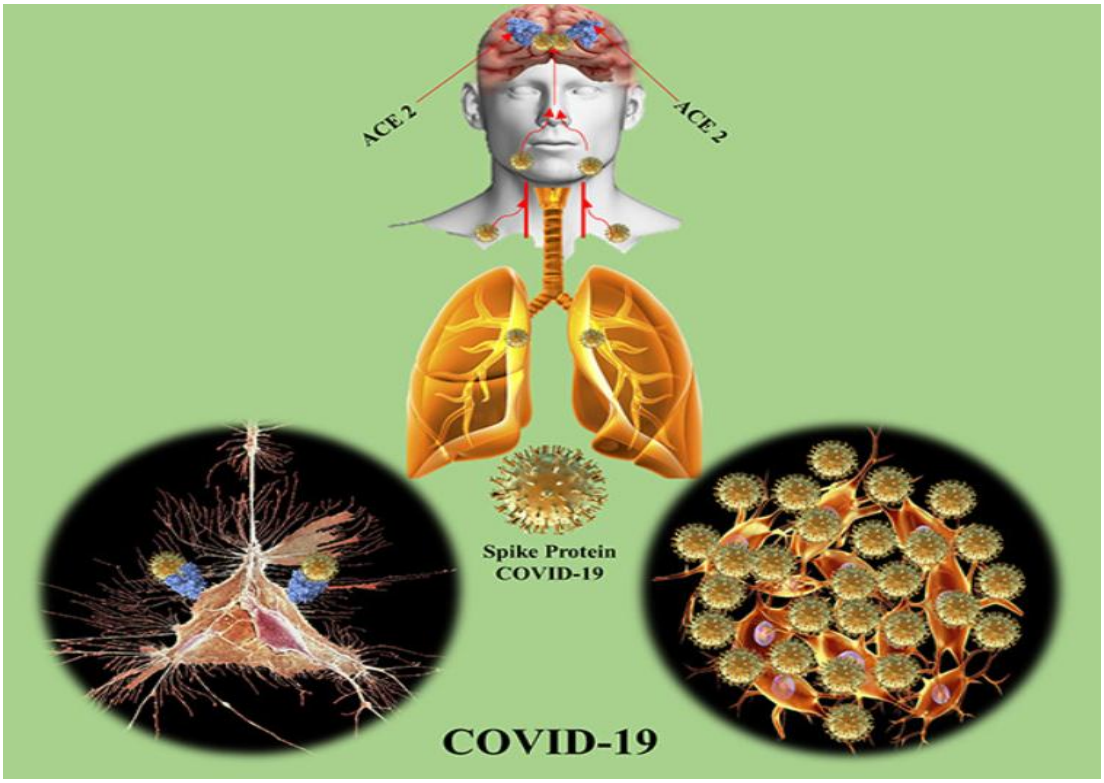

Figure 7: Interaction of COVID-19 with brain ACE-2 (Baig et al., 2020, Palasca et al., 2018).

CONCLUSION

Respiratory failure is the main symptom of coronavirus-19 disease condition, which is caused by several different machanisms i.e SARS-CoV-2 entry and replication, antigen presentation, humoral and cellular immunity, cytokine storm, immune evasion. Apart from respiratory failure coronavirus also causes the cardiovascular, enteric, neurological, and liver related dysfunction by acting on respective organs. However further investigations in to these mechanisms will help in development of better therapies for the management and treatment of COVID-19 infection.

REFERENCES

1. ALHOGBANI, T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. *Annals of Saudi medicine*, 2016; 36: 78-80
2. BADAWI, A. & RYOO, S. G. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *International Journal of Infectious Diseases*, 2016; 4**9:** 129-133.

3. BAIG, A. M., KHALEEQ, A., ALI, U. & SYEDA, H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS chemical neuroscience,* 2020.
4. BOSSART, K. N., WANG, L.-F., FLORA, M. N., CHUA, K. B., LAM, S. K., EATON, B. T. & BRODER, C. C. Membrane fusion tropism and heterotypic functional activities of the Nipah virus and Hendra virus envelope glycoproteins. *Journal of Virology,* 2002; 76: 11186-11198
5. CHAI, X., HU, L., ZHANG, Y., HAN, W., LU, Z., KE, A., ZHOU, J., SHI, G., FANG, N. & FAN, J. 2020. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv*.
6. DE WIT, E., VAN DOREMALEN, N., FALZARANO, D. & MUNSTER, V. J. 2016. SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology,* 14**:** 523.
7. FENG, G., ZHENG, K. I., YAN, Q.-Q., RIOS, R. S., TARGHER, G., BYRNE, C. D., VAN POUCKE, S., LIU, W.-Y. & ZHENG, M.-H. COVID-19 and liver dysfunction: Current insights and emergent therapeutic strategies. *Journal of Clinical and Translational Hepatology*, 2020; 8: 18.
8. GE, X.-Y., LI, J.-L., YANG, X.-L., CHMURA, A. A., ZHU, G., EPSTEIN, J. H., MAZET, J. K., HU, B., ZHANG, W. & PENG, C. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature,* 2013; 503: 535-538.
9. GLOWACKA, I., BERTRAM, S., MÜLLER, M. A., ALLEN, P., SOILLEUX, E., PFEFFERLE, S., STEFFEN, I., TSEGAYE, T. S., HE, Y. & GNIRSS, K. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *Journal of virology*, 2011; 85: 4122-4134.
10. GU, J., HAN, B. & WANG, J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission. *Gastroenterology,* 2020.
11. GUAN, W.-J., NI, Z.-Y., HU, Y., LIANG, W.-H., OU, C.-Q., HE, J.-X., LIU, L., SHAN, H., LEI, C.-L. & HUI, D. S. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine,* 2020.
12. HEATH, L., VAN DER WALT, E., VARSANI, A. & MARTIN, D. P. Recombination patterns in aphthoviruses mirror those found in other picornaviruses. *Journal of virology,* 2006; 80**:** 11827-11832.

13. GLOWACKA, I., BERTRAM, S., MÜLLER, M. A., ALLEN, P., SOILLEUX, E., PFEFFERLE, S., STEFFEN, I., TSEGAYE, T. S., HE, Y. & GNIRSS, K. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *Journal of virology*, 2011; 85: 4122-4134.
14. GU, J., HAN, B. & WANG, J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission. *Gastroenterology*, 2020.
15. GUAN, W.-J., NI, Z.-Y., HU, Y., LIANG, W.-H., OU, C.-Q., HE, J.-X., LIU, L., SHAN, H., LEI, C.-L. & HUI, D. S. 2020. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*.
16. HEATH, L., VAN DER WALT, E., VARSANI, A. & MARTIN, D. P. Recombination patterns in aphthoviruses mirror those found in other picornaviruses. *Journal of virology*, 2006; 80: 11827-11832.
17. HOFFMANN, M., KLEINE-WEBER, H., SCHROEDER, S., KRÜGER, N., HERRLER, T., ERICHSEN, S., SCHIERGENS, T. S., HERRLER, G., WU, N.-H. & NITSCHE, A. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*.
18. HOFMANN, H., HATTERMANN, K., MARZI, A., GRAMBERG, T., GEIER, M., KRUMBIEGEL, M., KUATE, S., ÜBERLA, K., NIEDRIG, M. & PÖHLMANN, S. S protein of severe acute respiratory syndrome-associated coronavirus mediates entry into hepatoma cell lines and is targeted by neutralizing antibodies in infected patients. *Journal of virology*, 2004; 78: 6134-6142.
19. HUANG, C. Huang C, Wang Y, Li X, et al. *Clinical features of patients infected with*, 2019; 497-506.
20. HUANG, C., WANG, Y., LI, X., REN, L., ZHAO, J., HU, Y., ZHANG, L., FAN, G., XU, J. & GU, X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 2020; 395: 497-506.
21. IWATA-YOSHIKAWA, N., OKAMURA, T., SHIMIZU, Y., HASEGAWA, H., TAKEDA, M. & NAGATA, N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *Journal of virology*, 2019; 93: e01815-18.
22. KAWASE, M., SHIRATO, K., VAN DER HOEK, L., TAGUCHI, F. & MATSUYAMA, S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine

protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. *Journal of virology*, 2012; 86: 6537-6545.

23. KLEINE-WEBER, H., ELZAYAT, M. T., WANG, L., GRAHAM, B. S., MÜLLER, M. A., DROSTEN, C., PÖHLMANN, S. & HOFFMANN, M. Mutations in the spike protein of Middle East respiratory syndrome coronavirus transmitted in Korea increase resistance to antibody-mediated neutralization. *Journal of virology*, 2019; 93: e01381-18.
24. LEUNG, W. K., TO, K.-F., CHAN, P. K., CHAN, H. L., WU, A. K., LEE, N., YUEN, K. Y. & SUNG, J. J. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology*, 2003; 125: 1011-1017.
25. LI, F., LI, W., FARZAN, M. & HARRISON, S. C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science*, 2005; 309: 1864-1868.
26. LI, G., CHEN, X. & XU, A. Profile of specific antibodies to the SARS-associated coronavirus. *New England Journal of Medicine*, 2003a; 349: 508-509.
27. LI, R., QIAO, S. & ZHANG, G. Analysis of angiotensin-converting enzyme 2 (ACE2) from different species sheds some light on cross-species receptor usage of a novel coronavirus 2019-nCoV. *Journal of Infection*, 2020a; 80: 469-496.
28. LI, W., MOORE, M. J., VASILIEVA, N., SUI, J., WONG, S. K., BERNE, M. A., SOMASUNDARAN, M., SULLIVAN, J. L., LUZURIAGA, K. & GREENOUGH, T. C. 2003b. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426: 450-454.
29. LI, X., GENG, M., PENG, Y., MENG, L. & LU, S. Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis*, 2020b.
30. LIU, J., WU, P., GAO, F., QI, J., KAWANA-TACHIKAWA, A., XIE, J., VAVRICKA, C. J., IWAMOTO, A., LI, T. & GAO, G. F. Novel immunodominant peptide presentation strategy: a featured HLA-A* 2402-restricted cytotoxic T-lymphocyte epitope stabilized by intrachain hydrogen bonds from severe acute respiratory syndrome coronavirus nucleocapsid protein. *Journal of virology*, 2010; 84: 11849-11857.
31. LU, R., ZHAO, X., LI, J., NIU, P., YANG, B., WU, H., WANG, W., SONG, H., HUANG, B. & ZHU, N. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, 2020; 395: 565-574.
32. MENACHERY, V. D., SCHÄFER, A., BURNUM-JOHNSON, K. E., MITCHELL, H. D., EISFELD, A. J., WALTERS, K. B., NICORA, C. D., PURVINE, S. O., CASEY, C. P. & MONROE, M. E. MERS-CoV and H5N1 influenza virus antagonize antigen

presentation by altering the epigenetic landscape. *Proceedings of the National Academy of Sciences,* 2018; 115: E1012-E1021.

33. NETLAND, J., MEYERHOLZ, D. K., MOORE, S., CASSELL, M. & PERLMAN, S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of virology,* 2008; 82: 7264-7275.
34. PALASCA, O., SANTOS, A., STOLTE, C., GORODKIN, J. & JENSEN, L. J. 2018. TISSUES 2.0: an integrative web resource on mammalian tissue expression. *Database,* 2018.
35. RAJ, V. S., MOU, H., SMITS, S. L., DEKKERS, D. H., MÜLLER, M. A., DIJKMAN, R., MUTH, D., DEMMERS, J. A., ZAKI, A. & FOUCHIER, R. A. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature,* 2013; 495: 251-254.
36. SIMMONS, G., GOSALIA, D. N., RENNEKAMP, A. J., REEVES, J. D., DIAMOND, S. L. & BATES, P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proceedings of the National Academy of Sciences,* 2005; 102: 11876-11881.
37. TURNER, A. J., HISCOX, J. A. & HOOPER, N. M. ACE2: from vasopeptidase to SARS virus receptor. *Trends in pharmacological sciences,* 2004; 25: 291-294.
38. WU, F., ZHAO, S., YU, B., CHEN, Y.-M., WANG, W., SONG, Z.-G., HU, Y., TAO, Z.-W., TIAN, J.-H. & PEI, Y.-Y. A new coronavirus associated with human respiratory disease in China. *Nature,* 2020a; 579: 265-269.
39. WU, J. T., LEUNG, K. & LEUNG, G. M.. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet,* 2020b; 395: 689-697.
40. WU, Q., ZHOU, L., SUN, X., YAN, Z., HU, C., WU, J., XU, L., LI, X., LIU, H. & YIN, P. Altered lipid metabolism in recovered sars patients twelve years after infection. *Scientific reports,* 2017; 7: 1-12.
41. XU, Z., SHI, L. & WANG, Y. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published online ahead of print February 18, 2020]. *Lancet Respir Med*.
42. XU, Z., SHI, L., WANG, Y., ZHANG, J., HUANG, L., ZHANG, C., LIU, S., ZHAO, P., LIU, H. & ZHU, L. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet respiratory medicine,* 2020; 8: 420-422.

43. YEAGER, C. L., ASHMUN, R. A., WILLIAMS, R. K., CARDELLICHIO, C. B., SHAPIRO, L. H., LOOK, A. T. & HOLMES, K. V. Human aminopeptidase N is a receptor for human coronavirus 229E. *Nature*, 1992; 357: 420-422.
44. ZHANG, H., KANG, Z., GONG, H., XU, D., WANG, J., LI, Z., CUI, X., XIAO, J., MENG, T. & ZHOU, W. 2020. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv*.
45. ZHENG, Y.-Y., MA, Y.-T., ZHANG, J.-Y. & XIE, X. 2020. COVID-19 and the cardiovascular system. *Nature Reviews Cardiology***,** 1-2.
46. ZHOU, P., YANG, X.-L., WANG, X.-G., HU, B., ZHANG, L., ZHANG, W., SI, H.-R., ZHU, Y., LI, B. & HUANG, C.-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020; 579: 270-273.