

## Research Article

# SARS-CoV-2 infection and phylogenetic analysis with the risk factors in human body alongside the pulmonary effects and medication

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## Abstract

Related the extremely transmittable abilities of SARS-CoV-2, a harmonious virus to the bat CoV, gets transmitted by three principal processes-- the inhalation of droplets from the SARS-CoV-2 infected person, contacting to the person, and by the surfaces and materials defiled with the virus. Whereupon bat Coronavirus is mostly like the pandemic causing virus SARS-CoV-2, bats are often deliberated and figured out as a possible primary host although no intermediate has not been defined yet in the wherewithal of transmission. The Spike Glycoprotein plays an important role in the case of penetration with the assistance of the ACE2 receptor and the Receptor Binding Domain. In the human body, infiltrating the nucleic acid into host cells, SARS-CoV-2 attacks one cell and one by one into the whole human body; therefore, infected cases are found symptomatic and asymptomatic considering the immune power. Patients with cardiovascular disease or diabetes proceed with their treatment with ACE2 often; therefore, there might be a high chance of getting infected. Whereas the SARS-CoV-2 infects the blood and then lungs, Antigens improvement can be better in order to avoid high-complicated effects. Currently, no vaccination or no accurate cure and treatment has not been defined. An explanation with analysis on SARS-CoV-2 has been performed from the aspect of virology, immunology and molecular biology. Several relevant figures have been included hereby in order to a better understanding of the very concept.

## Introduction

Ahmed Yesvi Rafa, et al., in these days introduced those zoonotic coronaviruses which have been still now found in the world, among them, bat coronavirus has the most and highest transmission and diffusion power. Therefore, avoiding having wild animals along with bat meats, animal to humanly transmit diseases in the future can be controlled and obviously there will be no chance for human- to- human transmission while

diseases will not appear from animals to humans although it will contain approximately the same types of the gene in the cell of the animals [1].

## Methodology

- Analysis of the pulmonological effects and other body organs' effects with the observation from the perspective of biology and virology.

## More Information

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**Keywords:** SARS-CoV-2; Biological fluid; Penetration; Pulmonary; Zoonotic



- How the SARS-CoV-2 infection occurred or viral transmission happened with the spreading activities in accordance with transmission wherewithal?
- Advantages and usages of Biological Fluid-Plasma Therapy with the vigor analysis of research articles
- A list of references has been referred based on the information collection, exact referral of research articles' and other investigations' citation has been included hereby.

## Results and discussion

### From literature, it has been found

Sulaiman Khan, et al. nowadays revealed that the pandemic causing Hunan Sea Food Market, Wuhan, China originated SARS-CoV-2's mutation and sequence introduced the bat as its primary or key host in transmission while no intermediate host has not been revealed. Intermediate host has not been determined yet. From the dark, the transmission Spike Glycoprotein with the assistance of RBD of Beta CoV is the principal role player of fast and rapid transmission. Phylogenetic observation confirmed that it has sequences similarities with the bat CoV- approximately 96.2% likeness accordingly clinical research.

Clinical research also confirmed that Remdesivir is highly dignified at the way to a better cure of the SARS-CoV-2 infection [6].

Rafa, et al. mentioned that the disastrous virus- SARS-CoV-2, which has currently turned into a pandemic, is a whole new strain of coronaviruses. A huge mystery lies behind its origin, whether it's zoonotic or made by humans, deliberately or accidentally. Scientists throughout the world are racing to determine the proper vaccine and treatment against the virus. SARS-CoV-2, a threat to the human race, is evolving its genome characteristics. So, the best thing is preventing it from following the measured steps and staying away from natural reservoirs of viruses, which will help us save ourselves from this situation and remain safe from this type of dangerous infection in the future [8].

Dr. Damiano Pizzol, et al. recently introduced that a chronic pulmonological and pneumonia based disease had been found in Wuhan, China and within a very short while, sequence analysis revealed the presence of SARS-CoV-2, a novel CoV. SARS-CoV-2 has been confirmed as the largest RNA Coronavirus- 30-32 kilobases sphere with zoonotic-natural origin. Sometimes, it blocks the immune system. Actually, the virus passes through larynx mucosa, then to lungs. Pharmacological researches revealed that with the assistance of Azithromycin, Glucocorticoids Remdesivir, Chloroquine and hydroxychloroquine, Tocilizumab, Lopinavir-ritonavir. Although it has several acts with the protein, the envelope, RBD, Spike Glycoprotein (in virus component) and ACE2

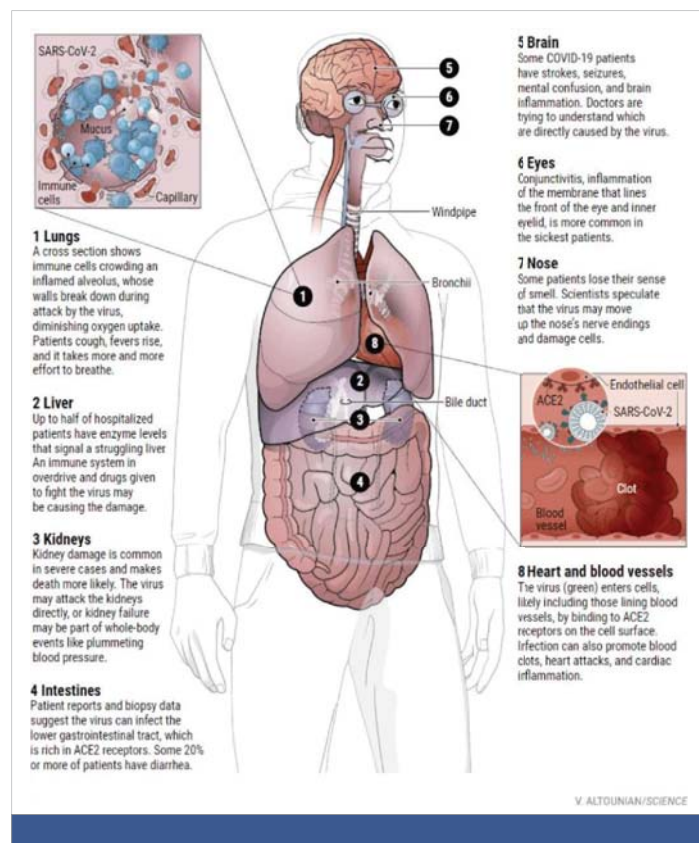
receptor (in human host cell) is strongly responsible for the comprehensive and rapid transmission. In the case of detection of SARS-CoV-2 infection, RT-PCR methods are highly recommended in order to determine the positive nucleic acid [16].

### SARS-CoV-2 infection process

The presence of animals has been defined in the case of rapid transmission of SARS-CoV-2. Experiment with K18 by delivering ACE2 highly revealed that the penetration occurs by the assistance of K18 and by the outing or expression of ACE2 from its receptor. In addition to the RBD with the spike glycoprotein, the fast transmission occurs, and then like before, by ACE2 and K18, human body cells get infected and then all the body and obviously, firstly it infects the lungs. Consequently, lungs get most infected by SARS-CoV-2 infection and penetration in the human body [7].

SARS-CoV-2 creates a very respiratory viral disease. Since it infects the respiratory system, the lung gets affected most. SARS-CoV-2 acts with an accurate host cell receptor that is called.

ACE2 Receptor for infiltrating into the other cells and into those cells. That ACE2 is expressed by the lungs, nose, blood, and sometimes from the brain. Consequently, the virus enters into the host cell and they multiply themselves and make a huge number in quantity. In fact, when the virus attacks the human body and its cells extremely, critical effects and body synchronizations occur. Considering the immune system, its





power, and the positive acts of Antigens, an asymptomatic or symptomatic situation took place then. While there is a good immune power with antigens, asymptomatic cases mostly and on the contrary, the dissimilar function can be seen mostly. Patients of diabetes and cardiac disease make the treatment with ACE2 and they have immune strength. That's why having less immunity alongside treating with ACE2, thereby they have a high chance of getting infected and then ACE2 helps to continue the penetration and infection into the human body [11].

### Origin of SARS-CoV-2

Bats are the hosts of some *Beta coronaviruses* and *Alpha Coronaviruses* that includes SARS-CoV and MERS-CoV and other human coronaviruses like HCoV-NL63. Avian species are the origin of *Gamma Coronaviruses* and *Delta Coronaviruses* but infect both avian and mammal animals. Viruses that originate from bats are normally transmitted into humans through intermediate hosts. Such as, MERS-CoV has originated from bats but has got human contact through dromedary camels as the intermediate host. As well as, raccoon dogs and palm civets are the intermediate hosts of SARS-CoV and SARS-CoV-2 respectively [9].

Presently, the Chinese government reported WHO about many people infected by a new kind of pneumonia in December 2019. More than 50 people were infected rapidly after the outbreak caused by the Huanan seafood market in Wuhan city of China. Live animals, such as dogs, snakes, civets, marmots, bats, rabbits, birds, and frogs. Suggesting viral pneumonia, the National Health Commission of China informed more details on the epidemic on 12<sup>th</sup> January 2020. This virus was identified as a novel coronavirus, through the sequence-based analysis of isolates from the infected. By the by, it was later found that many people infected by the novel coronavirus probably have visited live animal markets and some others have taken infected animals or birds as food. But more investigation explained that several people have been infected though they didn't have any history of going to the seafood market. Thus, it confirmed the human-to-human spreading capability of this virus [10].

### Phylogenetic analysis

SARS-CoV-2 originates from the *Coronaviridae* family and *Ortho Coronaviridae* subfamily. *Alphacoronavirus*, *Beta coronavirus*, *Gamma coronavirus*, and *Delta coronavirus*: are the 4 genera. Among the coronaviruses, SARS-CoV, MERS-CoV and SARS-CoV-2 are all *Beta Coronaviruses*, one of the genes in which many viruses are included which infects bats, humans and other animals, wild and domestic. [9]

At the early stage of the outbreak, full-length genome sequence was collected from 5 patients [17].

The present emergence in the world, SARS-CoV-2, is suspected to be transmitted into humans through zoonotic

origins. Bat is the most probable host of the virus, as it is a huge natural reservoir of deadly viruses and bacteria. As this strain of coronavirus has similarity with MERS-CoV, thus the origin of MERS-CoV, bat, is considered as its zoonotic origin [10].

To know about the relation between bat CoV and SARS-CoV-2, phylogenetic analysis of all the genomes of bat coronaviruses were performed. And to find the intermediate host, phylogenetic analysis on the coronavirus genes of the animals that were marketized in the Chinese markets was also done. Mutation process was also tested to figure out what has helped the virus to penetrate into the human host. After the phylogenetic analysis, if the phylogenetic tree is reconstructed with different coronavirus strains, it is observed that SARS-CoV-2, bat RaTG13 and pangolin CoV genes cluster in a monophyletic order, from which we can understand that pangolins has the most possibility of being an intermediate host, and bats to be the primary reservoirs. An analysis of Rafael dos Santos Bezerra, et al. proves the specificity of SARS-CoV-2 as a bat CoV and also puts forward the possibility of pangolins to be the intermediate host [19].

As the intermediate host of SARS-CoV-2, Malayan pangolins are the most suspected. It is evident from the spread of earlier SARS-CoV that some wild animals may also be involved in the spread of this disease also. In Wuhan, the first cases were related to the seafood market where live animals were sold. By the way, many mammals were found to be sold there. As the market was closed just after the disease broke out, it was difficult to investigate thoroughly about the zoonotic origin.

From an experiment, Tommy Tsan-Yuk Lam, et.al. Investigated frozen samples of 18 Malayan Pangolins (*Manis Javanica*). These are one of the endangered mammal species and are highly being trafficked as it is used as a food source and in many Chinese traditional medicines. For the experiment they received the lungs, intestines and blood samples and among the total 43 samples 6 had the presence of coronavirus within them. The samples had genomic organization just like SARS-CoV-2, and the genome sequence had a very high similarity of about 99%. Further testing was conducted through qPCR on other pangolin samples obtained between mid-2018. Among the 19 samples, that included lung, intestine and other tissues, 3 lung tissues and 3 separate pangolins were tested positive for coronavirus [18].

The SARS-CoV-2 got diffused from Hunan Seafood Market, Wuhan, China from the end of December, 2019. Having the experience from MERS, Spanish Flu, soon the public health system had recently been expanded [20].

### Pulmonary effects of SARS-CoV-2

COVID-19 or SARS-CoV-2 has a severe toll on the infected person's lung. It can cause complications in the lung, namely Pneumonia, and in extreme cases ARDS [acute respiratory



distress syndrome]. Another complication caused by COVID-19, Sepsis is causing long-lasting harm to the infected person's alveolus. Even before the onset of the global pandemic, Sepsis caused nearly 50 million cases every year and is the reason for death for 1 in 5 newborn children worldwide. Usually, older people are more vulnerable to lung infections caused by COVID-19, since the tissues in their lungs are much more rigid due to their age [2].

When affected by Pneumonia, the lungs of the patient get filled with fluid. Severe cases can see them get inflamed, in turn leading to difficulties in breathing, even requiring the use of ventilators or oxygen tanks to stabilize the patient. Pneumonia caused by COVID-19 usually takes place in both of the lungs of the human body. The upper and lower part of our respiratory tract can get infected by COVID-19. As it travels down the airways, the lining can become inflamed and irritated. Cases have also spiraled up where the infection has reached the patient's alveoli. As a result, the air sacs of the lungs might get filled with fluids, severely outstretching and limiting their ability in taking oxygen, resulting in shortness of breath. Patients with Diabetes, high blood pressure tend to be in a more critical situation. The usual Pneumonia does not cause long-lasting damages in most cases, but in COVID-19, Pneumonia causes severe damages in the lungs that might take months to improve [2].

Pneumonia related to COVID-19 can cause blood leakage in the tiny blood vessels around the lungs. The leaked blood gradually fills the air sacs with fluids, causing disruptions in breathing. Furthermore, shortness of breath sets in, causing ARDS [Acute Respiratory Distress Syndrome], which is described by many institutions as a form of lung failure. Artificial ventilation is often required by patients suffering from ARDS. Another pulmonary disease caused by COVID-19 is Sepsis, which spreads through the bloodstream, may cause tissue damage severely [3].

Seeing the severity of lung diseases caused by COVID-19, prominent institutions have devised three prominent factors causing lung damage. They are as follows-

1. The first is identifying the severity of the infection, finding out whether the person has a timid, mild or severe case. The more severe a case is, the more likely it is of leaving long-lasting damage on the patients' pulmonary system.
2. The second thing that needs to be studied and found is, whether the patient has an existing health problem, say, COPD [Chronic Obstructive Pulmonary Disease] or any other type of disease that may increase the risk.
3. The final and most crucial factor, treatment. Doctors and researchers suggest appropriate treatment can drastically reduce the risk of long term damage to the lungs. Estimated recovery time for the lung damages might be around 3-12 months, after initial damage,

there is scarring. Over time, the tissues heal and the lungs go back to pre-COVID levels [5].

Researchers have found out that Smokers and has-been smokers have 1.91 times the odds of progression of COVID-19 than Non-Smokers. This study is certainly not that surprising, considering the adverse effects Smoking has on the Pulmonary Immune Function. Even though studies related to this are highly debated, taking into consideration the considerable addiction to smoking. But current shreds of evidence clearly show that assessed smokers have significantly increased chance of contracting a virus and consequently, spreading it [4].

The virus enters the cells of the lung airways via the angiotensin-converting enzyme receptor, which is a molecule that connects the inside and outside of our cells through the cell membrane. When this occurs, the immune system responds through an intense response, known as a cytokine storm. Also, the blood cells get clotted. All of this results in damage to lung cells. Then, our immune system replaces the damaged cells with scar tissue, which is dense. This results in a condition called "pulmonary fibrosis", which is seen in COVID-19 patients. This may result in breathlessness and hindrance and daily activities, which would otherwise, the infected person would accomplish easily. Drugs, reducing scarring, may help prevent or minimize this situation. The impacts of Pulmonary fibrosis are fairly unknown, it may lead to long term symptoms and a fall in the lung function [3].

Patients getting treated for COVID-19 can suffer from side effects. Even, their lungs might suffer from the treatment meant to heal it. Having undergone artificial ventilation, many may lose muscle mass, leaving their body weak even after their lungs having recovered. Older people may become destabilized even if they suffer from "mild" COVID-19 [4].

While most people who have contracted the virus will recover completely. Still, more people would be seen with pulmonary fibrosis or Long-lasting lung damage caused by ARDS or sepsis. These patients will still need antifibrotics, pulmonary rehabilitation, home oxygen therapy and regular check-ups. But, ultimately, the pulmonary immunity should be recovered within 1 year even if the case is critical [5].

### Biological fluid

This subject revolves around the central role of airborne virus transmission through the viral particles released in the air by an infected person by speaking, sneezing, coughing or even breathing. The droplets released during speaking generated by asymptomatic disease vectors are also considered for their viral load and risk of infection. Through natural or artificial ventilation on the environment of the transmission, we can deduce that the risk of disease decreases as the viral loads start to dilute mixing with other particles with the air. But the contagion can still reach larger distances if aided by the forced ventilation [12].



Till now, the relation between the bodily fluids and Sars-Cov-2 has not been established and little pieces of evidence point towards transmission by bodily fluids. The ability of viral loads in entering the cell has become a crucial factor in characterizing the infection. It has been established that that viral loads bind to the angiotensin-converting enzyme 2 [ACE2] in the cells via it's spike proteins. Researchers have found a way of how COVID-19 infects the gastrointestinal tract. Which explains the infection and gastrointestinal symptoms. Recently, viral loads were also discovered in the urine, tears and conjunctival sections. Studies suggested that traces found in the reproductive organs of humans can lead to transmission of the virus through exchange of bodily fluids. But a more recent study, dismissed this having found no ACE2 receptors in the Cervix tissues. Furthermore, studies pointed out, that Sars-Cov-2 does not spread through the discharge during pregnancy and is also absent in the neonatal throat swab, breast milk and amniotic fluids. But another study shows that Sars-Cov-2 CAN infect the fetal liver during pregnancy. So far, the transmission through blood has been theoretical and minimal [13,14].

Some recent studies have pointed out how COVID-19 causes blood vessel damage. The researchers who conducted the study compared the lungs of deceased influenza patients and deceased COVID-19 patients. The researchers found an interesting disease pattern. The viral loads infiltrated the endothelial cells, causing a blood clot. COVID-19 had 9 times the thrombosis than regular Flu. The virus causes unusual growth of blood vessel. These clots not only damage the lungs but can be lethal and even damage the brain, heart. These clots are relative to the damaged blood vessels by the viral loads. The damage triggers a healing mechanism from the body itself known as intussuscepted angiogenesis. When infected by COVID, this natural reaction is seen 30 times greater than normal. The blood vessels respond to any injury by producing a whole new structure and network of healing blood vessels. Studies show the more intussuscepted angiogenesis is present, the longer the patient has to be hospitalized. So, the blood vessel damage is not only directly linked but also crucial in dictating the severity of COVID-19 disease [13,15].

### Transmission of SARS-CoV-2

COVID 19 spreads through active and passive contact or close contact with an infected person. Mouth and nose secretions, including saliva, secretion droplets, and respiratory secretions, may carry the viral loads. When an infected person coughs or sneezes, the viral loads are released from the mouth and the nose, traveling up to 1 meter away. Transmissions can occur when coming in contact with infected surfaces because of the spread of fomites. The infection will happen when someone touches the contaminated surfaces and then touches their mouth or nose without washing hands [23,24].

Aerosolized droplet nuclei can stray in the air for long

periods. These aerosols may contain the viral load of SARS-Cov-2. If this enters the lungs of a healthy person, they might get contracted by the virus. As the droplets stay suspended in the air for quite some time, closed places have more chance of transmitting them as the droplets cannot disperse in the air as quickly as open places. This explains why closed settings like clubs, bars, places of worship, and work have become the epicenter of the virus. Here, aerosol transmission takes place, owing to the inadequate ventilation and indoor crowd [24].

So, the main three modes of transmission are through droplets, aerosol transmission, and fomites.

1. The first and most widespread mode of transmission is transmitted through droplets. These droplets may be secreted through saliva and respiratory secretions. Droplets, which are >5-10  $\mu\text{m}$  in diameter, are respiratory droplets and smaller than that are known as droplet nuclei or aerosols. These droplets can stay suspended in the air for quite some time, travelling up to 1 meter [23].
2. The spread of an infectious agent caused by the circulation of droplet nuclei is airborne transmission. Studies have shown that the generated aerosols can stay from 3-16 hours suspended under stabilized laboratory conditions. Studies conducted at some health care settings have reported the presence of SARS-CoV-2 RNA in the air. This aerosols may explain the super spreading event taking place in various clustered places [25].
3. The third prominent way of transmission is Fomite transmission. Respiratory secretions secreted by infected individuals can pollute various surfaces and objects. Fomites or contaminated surfaces is produced in this manner. Viral loads can be detected on these surfaces for long times. A healthy person can get infected by touching the objects used by an infected person, say objects like stethoscope or thermometer, followed by the touching of their mouths and noses [26,27].

As described earlier, the transmission of viral loads through blood is minimal, but still theoretically possible. And bodily fluids can even play a role in communication, considering traces of viral loads have been found in the urine and feces of the infected person. Also, the virus may spread from an infected person even if he has no symptoms. That's why testing can isolate such cases [27].

### Conclusion

SARS-CoV-2(Severe Acute Respiratory Syndrome-Coronavirus-2), which has a very complicated life cycle with the exceeding mutation acts, its mutational analysis revealed that bat is the primary host in transmission while intermediate



host is undetermined. Clinical retrieves introduced that biological fluid is quite acceptable as a cure. On the contrary, currently no vaccines have not been revealed. By expressing the ACE2 with the RBD & Glycoprotein, the penetration process occurs. SARS-CoV-2 impacts the respiratory system and the other related blood, lungs, cells etc. Age also varies in the consideration of curity. ACE2 is used in the treatment of several diseases, so it assists in order to get infected. Actually, viruses which have originated from bats, have been transmitted by any intermediate. Investigations by National Health Commissions of China strongly confirmed that 50 people were rapidly infected who had been to the sea food market then and it was introduced as an epidemic on the 12th January, 2020. But in some cases, it had been established that some people who had not visited the market, were also infected and that circumstance confirmed the Human-Human Transmission. Whereas SARS-CoV-2 principally attacks the lungs of the human body as a respiratory viral disease originated from zoonotic coronavirus, it also affects the other related body components- blood vessels, brain etc of the human body. A study from Cambridge University introduced that punctured lungs are sometimes seen in those people who were affected by the disease. When the immunity strength gets lessened by the infection of SARS-CoV-2 in the human body, chronic pneumonia, high fever, coughing, headache, diarrhea are seen as its signs and symptoms along with the risk factors. Actually, when the fluid fills the lungs, chronic and critical pneumonia can be seen. As the wherewithal of the transmission of the virus three principal factors have been detected- Inhalation of droplets from the infected person, getting touched with the surface contained in SARS-CoV-2 and obviously, contacting or getting touched with any infected person. While researchers and scientists all over the world are trying hard to reach the accurate and estimated vaccine of SARS-CoV-2 infection, in the meantime, Plasma-therapy as Biological Fluid has demonstrated the light of saving lives. Considering the variance of ages and immune system, that very biological fluid is one of the most reliable cures to cure the infection as long as they will be unable to reach the exact preventive vaccine.

## Acknowledgement

This very research paper has been prepared through the vigor of research articles and informative materials. And other research related sources- research contents and books with its bibliographies have also been included hereby.

## References

- Rafa AY, Luisetto M, Musa N, Arif OB, Ilman A, et al. A Study on SARS-CoV-2 Penetration Process and Pathogenesis Analysis based on the Biological Mechanism as well as Medication to Alleviate the Impacts on Human Body. *Adv Bioengin Biomed Sci Res.* 2020; 3: 92-100. <https://www.opastonline.com/storage/2020/09/a-study-on-sars-cov-2-penetration-process-and-pathogenesis-analysis-based-on-the-biological-mechanism-as-well-as-medication-to-alleviate-the-impacts-on-human-body-abbsr-20.pdf>
- Potus F, Mai V, Leuret M, Malenfant S, Breton-Gagnon E, et al. Novel insights on the pulmonary vascular consequences of COVID-19. *Am J Physiol Lung Cell Mol Physiol.* 2020; 319: L277-L288. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32551862/](https://pubmed.ncbi.nlm.nih.gov/32551862/)
- McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology.* 2020; 2: e437-e445. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32835247/](https://pubmed.ncbi.nlm.nih.gov/32835247/)
- Patanavanich R, Glantz SA. Smoking is associated with COVID-19 progression: A meta-analysis. *Nicotine Tob Res.* 2020; 22: 1653-1656. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32399563/](https://pubmed.ncbi.nlm.nih.gov/32399563/)
- Liu X, Long C, Xiong Q, Ma J, Chen C, et al. Association of renin-angiotensin-Aldosterone system inhibition with risk of COVID-19, inflammation level severity and death in patients with COVID-19: A rapid systematic review and meta-analysis. 2020.
- Shahreem MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristic of human coronaviruses. *J Adv Res.* 2020; 24: 91-98. [PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7113610/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7113610/)
- Winkler ES, Bailey AL, Kafai NM, et al. SARS-CoV-2 Infection of Human ACE2-transgenic Mice Causes Severe Lung Inflammation and Impaired Function. *Nat Immunol.* 2020; 21: 1327-1335. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32839612/](https://pubmed.ncbi.nlm.nih.gov/32839612/)
- Rafa AY, Luisetto M, Musa N, Arif OB, Ilman A, et al. A Study on the Biological Mechanism of SARS-CoV-2, its Impacts, and Adversities on the Human Body and Medication to Alleviate its Impacts. *Virology & Mycology.* 2020; 9: 192 <https://www.longdom.org/abstract/a-study-on-the-biological-mechanism-of-sarscov2-its-impacts-and-adversities-on-the-human-body-and-medications-to-alleviate-57704.html>
- Perlman S. Another Decade, Another Coronavirus. *NEJM.* 2020; 382: 760-762. <https://www.nejm.org/doi/full/10.1056/NEJMe2001126>
- Jaimes JA, André NM, Chappie JS, Millet JK, Whittaker GR. Phylogenetic Analysis and Structural Modeling of SARS-CoV-2 Spike Protein Reveals an Evolutionary Distinct and Proteolytically Sensitive Activation Loop. *J Mol Biol.* 2020; 432: 3309-3325 [PubMed: https://pubmed.ncbi.nlm.nih.gov/32320687/](https://pubmed.ncbi.nlm.nih.gov/32320687/)
- Burke CW. Coronavirus Transmission: Where the Virus Goes in your Body and How it is Spread? *Biospace.* 2020. <https://www.biospace.com/article/all-the-ways-we-know-that-you-can-get-coronavirus/>
- Xiong Y, Liu Y, Cao L, Wang D, Guo M, et al. Transcriptomic characteristics of Bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg Microbes Infect.* 2020; 9: 761-770. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32228226/](https://pubmed.ncbi.nlm.nih.gov/32228226/)
- Seminara G, Carli B, Forni G, Fuzzi S, Mazzino A, et al. Biological fluid dynamics of airborne COVID-19 infection. *R endiconti Lincei. Scienze Fisiche e Natural.* 2020; 31: 505-537.
- Mohseni AH, Taghinezhad SS, Xu Z, Fu X. Body fluids may contribute to human-to-human transmission of severe acute respiratory syndrome coronavirus 2: Evidence and practical experience. *Chin Med.* 2020; 15: 58. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32514291/](https://pubmed.ncbi.nlm.nih.gov/32514291/)
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, et al. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in COVID-19. *New Eng J Med.* 2020; 383: 120-128. [PubMed: https://pubmed.ncbi.nlm.nih.gov/32437596/](https://pubmed.ncbi.nlm.nih.gov/32437596/)
- Di Gennaro F, Pizzolo D, Marotta C, Antunes M, Racalbutto V, et al. Coronavirus Diseases (COVID-19) Current Status and Future Perspectives: A Narrative Review. *Int J Environ Res Public Health.* 2020; 17: 2690; [PubMed: https://pubmed.ncbi.nlm.nih.gov/32295188/](https://pubmed.ncbi.nlm.nih.gov/32295188/)
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579: 270-273.



18. Lam TT, Jia N, Zhang Y. et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature*. 2020; 583: 282–285  
**PubMed:** <https://pubmed.ncbi.nlm.nih.gov/32218527/>
19. dos Santos B, Valença, IN, de Cassia Ruy, P, et al. The novel coronavirus SARS-CoV-2: From a zoonotic infection to coronavirus disease-2019. *J Med Virol*. 2020; 1– 9.
20. Marc L, Swerdlow, David L. and Finelli, Lyn. Defining the Epidemiology of COVID-19 — Studies Needed. *New Zealand J Med*.2020; 382: 1194-1196.  
**PubMed:** <https://pubmed.ncbi.nlm.nih.gov/32074416/>
21. Sajadi MM, Habibzadeh P, Vintzileos A, Shokouhi S, Miralles-Wilhelm F, et al. Temperature and latitude analysis to predict potential spread and seasonality for COVID-19. *S SRN Electronic J*. 2020.
22. Morawska L, Tang JW, Bahnfleth W, Bluysen PM, Boerstra A, et al. How can airborne transmission of COVID-19 indoors be minimised? *Environ Int*. 2020; 142: 105832.  
**PubMed:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250761/>
23. Rocklöv J, Sjödin H. High population densities catalyse the spread of COVID-19. *J Travel Med*. 2020; 27:  
**PubMed:** <https://pubmed.ncbi.nlm.nih.gov/32227186/>
24. Tindale L, Coombe M, Stockdale JE, Garlock E, Lau WY, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. 2020.
25. Dehning J, Zierenberg J, Spitzner FP, Wibral M, Neto JP, et al. Inferring change points in the spread of COVID-19 reveals the effectiveness of interventions. *Science*. 2020; 369: eabb9789  
**PubMed:** <https://pubmed.ncbi.nlm.nih.gov/32414780/>
26. Wadman M, Couzin-Frankel J, Kaiser J, Maticic C. How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. *Science*. 2020.
27. <https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes>