World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Review Article

ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2024
Volume: 3; Issue: 1
Page: 38-51

CONFLUENCE OF RESPIRATORY CHALLENGES: INVESTIGATING THE RELATIONSHIP BETWEEN ASTHMA, ALLERGIES AND COVID -19

Rubi Yadav*, Pratixa Patel, Sejal Khuman, Tiwari Pooja and Mishra Satyam

Post Graduate Student, Rofel Shri G. M. Bilakhia College of Pharmacy, Vapi, Gujarat, 396191, India.

Article Received: 04 December 2023 | | Article Revised: 27 December 2023 | | Article Accepted: 16 January 2024

Corresponding Author: Rubi Yadav
Post Graduate Student, Rofel Shri G. M. Bilakhia College of Pharmacy, Vapi, Gujarat, 396191, India.

ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (sars-cov-2) is the cause of the global pandemic disease known as coronavirus disease 2019 (covid-19), and abnormal, overactive innate immunity and "cytokine storms" have been proposed as potential pathological mechanisms for the disease's rapid spread. Theoretically, asthmatic individuals should be more vulnerable to and more severely affected by sars-cov-2 infection due to a weak immune response to the virus and a propensity for exacerbation brought on by common respiratory viruses. It is important to identify the risk and protective factors that affect the severity of the covid-19 asthma condition. Asthma hasn't been found to be a substantial risk factor for covid-19 disease, though. The angiotensin-converting enzyme 2 (ace2) receptor, which is present in a number of human organs, allows sars-cov-2 to infect host cells. But lower ace2 expression in airway cells is linked to asthma and respiratory allergies. Additionally, the use of inhaled corticosteroids for the management of asthma is connected to reduced ace 2 receptor expression, asthma thereby reduces covid 19 morbidity and sars-cov-2 infection susceptibility.

KEYWORDS: Ace2, Covid 19, Allergies and Asthma.

1. INTRODUCTION

1.1 Coronavirus

The largest known positive-sense RNA viruses, coronaviruses damage both human and animal health severely and have a wide spectrum of hosts. Low-pathogenicity coronavirus (CoV-229E, CoVNL63, CoV-OC43, and CoV-HKU1), which often causes mild to moderate sickness, and high-pathogenicity coronavirus, which can cause serious, potentially fatal infections, are coronaviruses that are known to infect people.[14] Severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks have had a significant negative influence on both socioeconomic and public health aspects in the twenty-first century.[1]

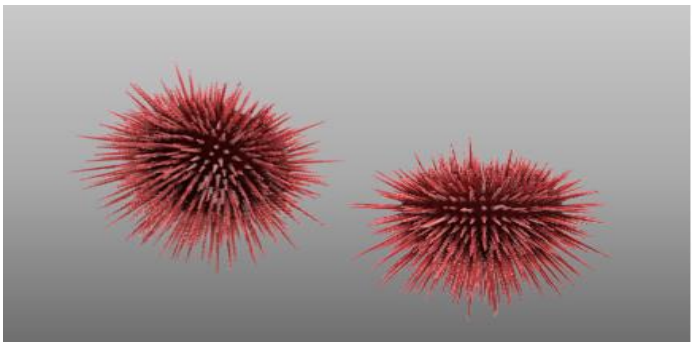

Figure 1: Transmission electron micrograph of organ cultured coronavirus OC43.

Early in December 2019, a new coronavirus illness known as SARS-CoV-2 started to circulate in Wuhan, China. Since then, it has quickly spread throughout the world. Coronavirus disease 2019 (COVID-19) is the name of the illness condition caused by this new coronavirus, and the World Health Organization designated this epidemic to be a pandemic on March 11, 2020. (WHO). Only 1,735,657 patients had recovered as of May 15, 2020, and there were 4,580,498 confirmed cases and 305,618 fatalities worldwide.[27] Compared to the SARS and Middle East respiratory syndrome (MERS) pandemics, which occurred in 2003 and 2013, respectively, these numbers are significantly higher, despite the fact that the mortality rate for COVID-19 is currently lower.[11] SARS-CoV-2 attaches primarily to angiotensin converting enzyme 2 (ACE2) receptors in host cells, which are prevalent in the heart, blood vessels, intestine, lungs, and other body organs. COVID-19 causes respiratory symptoms that can range from mild to severe, and a large proportion of patients go on to develop acute respiratory disease syndrome (ARDS). These severe symptoms are linked to a real cytokine storm, particularly IL-6, and one of the results can be death.

Significant risk factors for COVID-19 morbidity and mortality have been identified as old age and underlying morbidities, such as cardiovascular diseases, particularly hypertension and metabolic disorders (obesity and diabetes). COPD and asthma may not, however, be frequent comorbidities.[11]

1.2 CORONAVIRUS' STRUCTURE

Large, approximately spherical particles with distinctive surface projections are coronaviruses. Although their size varies greatly, they typically have an average diameter of 120 nm. Extreme sizes between 50 and 200 nm in diameter are known. They are contained in a shell that contains several protein molecules. When the virus is outside the host cell, it is shielded by the lipid bilayer envelope, membrane proteins, and nucleocapsid.

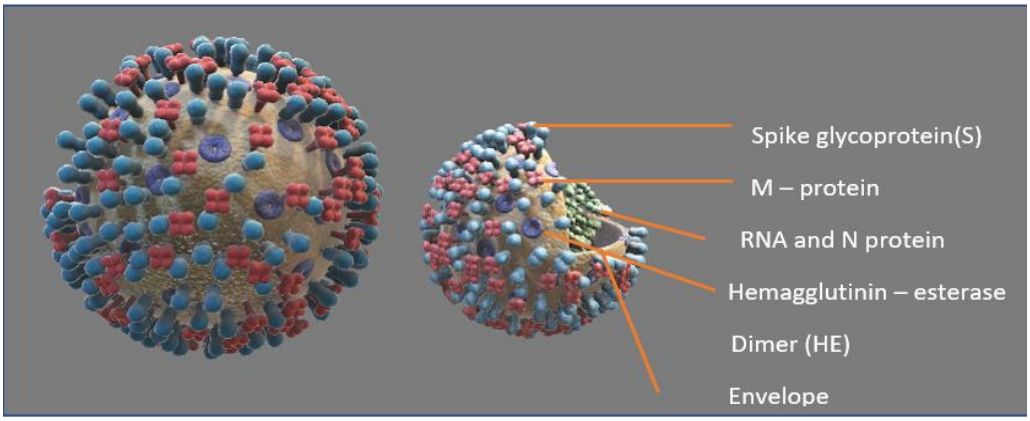

Figure 2: Structure of Coronavirus.

The membrane (M), envelope (E), and spike (S) structural proteins are embedded in the lipid bilayer that makes up the viral envelope. In the lipid bilayer, the E:S:M ratio is roughly 1:20:300. The structural proteins E and M work with the lipid bilayer to shape and preserve the size of the viral envelope. In order to connect with the host cells, S proteins are required. The M protein of the human coronavirus NL63, as opposed to the S protein, has the binding site for the host cell. The envelope has an 85 nm diameter.

The M protein, a type III membrane protein, is the primary structural protein of the envelope and gives it its overall form. The layer is 7.8 nm thick and made up of 218 to 263 amino acid residues.

The corona- or halo-like appearance is caused by the spikes, which are the coronaviruses' most distinctive feature. A coronavirus particle has 74 surface spikes on average. Each spike is made up of a fragment of the S protein and is roughly 20 nm long. Two S1 and S2 subunits make up the S protein in turn. The class I fusion protein homotrimer S mediates membrane fusion and receptor interaction between the virus and the host cell. The S1 subunit has a receptor binding domain and generates the spike's head. (RBD). When the protease is activated, the S2 subunit facilitates fusion by forming the stem that secures the spike in the viral envelope. Until they bind to the host cell membrane, the two subunits are exposed on the viral surface and remain noncovalently connected. Three S1 are joined to two S2 subunits in a functionally active state. When the virus attaches and fused with the host cell, the host cell's trans membrane protease serine 2 (TMPRSS2) and other proteases, such as the cathepsin family, separate the subunit complex into individual subunits.

The most important elements of an infection are S1 proteins. Due to their role in host cell specificity, they are also the most changeable elements. They have two primary domains, the N- and C-terminal domains (S1-NTD and S1-CTD, respectively), both of which are receptor-binding domains. The host cell's surface sugars are recognized by the NTDs and bound there. The MHV NTD, which interacts to a protein receptor called carcinoembryonic antigen-related cell adhesion molecule 1, is an exception. (CEACAM1). S1-CTDs are in charge of identifying numerous protein receptors, including dipeptide peptidase 4, amino peptidase N, and angiotensin-converting enzyme 2 (ACE2). (DPP4).

Additionally, a subset of coronaviruses called hem agglutinin esterase contains a shorter spike-like surface protein. These coronaviruses are precisely beta coronavirus subgroup A members. (HE). The HE proteins are 40–50 kDa in size and exist as homodimers made up of roughly 400 amino acid residues. In between the spikes, they appear as minute surface projections that are 5 to 7 nm long. They aid in both the attachment and separation from the host cell.

The nucleocapsid, which is found inside the envelope, is made up of several copies of the nucleocapsid (N) protein that are continuously beaded-on-a-string-like bound to the positive-sense single-stranded RNA genome. The N protein is a phosphoprotein that ranges in size from 43 to 50 kDa and has three conserved domains. The domains 1 and 2, which are typically enriched in arginine and lysine, make up the majority of the protein. Because there are more acidic amino acid residues than basic amino acid residues, domain 3 has a short carboxy terminal end and a net negative charge[11].

2. ROLE OF ACE- 2 IN COVID 19 DISEASES

2.1 STRUCTURE AND FUNCTION OF ACE2

In 2000, the 40 kb ACE2 gene on chromosomal Xp22 was first identified. A type I transmembrane glycoprotein of 805 amino acids, the human ACE2 protein is encoded.

With its N-terminus facing outward, ACE2 binds to the plasma membrane using a C-terminal tail that is short inside cells. The extracellular area is where ACE2's highly conserved catalytic site is located, allowing it to digest circulating peptides. The active catalytic site of ACE and ACE2 share 40% of the same sequence, however they have different substrate specificities. As a carboxypeptidase, ACE2 produces Ang (1-7) from Ang II and Ang (1-9) from Ang I, while ACE transforms the decapeptide Ang I into an octapeptide Ang II when it operates as a peptidyl dipeptidase.[30] The hormone system that regulates blood pressure homeostasis and fluid and salt balance, the renin-angiotensin system (RAS), is primarily controlled by Ang II.[2] Vasoconstriction is mediated by Ang II, which also leads to the overactivation of RAS, which is connected to a variety of illnesses such as hypertension, heart failure, and renal disease.[31] As a result, by blocking Ang II's actions, ACE2 is essential in keeping the RAS in its proper balance. Moreover, Ang A can be transformed by ACE2 into almandine, a cardiovascular system defender. Disintegrin and metalloproteinase 17 can cleave membrane-bound ACE2 to release the soluble version, which may act as a competitive interceptor of ACE2's binding ligands.[15] To promote tissue damage in the lung, Ang II can cause bronchoconstriction, vasoconstriction, fibroproliferation, cytokine production, and cell death. According to reports, ACE2 acts as a negative regulator of Ang II and guards the lung against harm (Figure 3).

The absence of ACE2 expression in the lung caused increased lung oedema, significant neutrophil buildup, and decreased lung function in the acute lung injury/acute respiratory distress syndrome paradigm.[32] In addition to acting as a peptidase to catalase the cleavage of Ang II under physiological conditions, ACE2 has been discovered to be a functional receptor for the SARS-CoV and is crucial for the progression of the disease following SARS-CoV infection. The S1 domain of the SARS-CoV spike protein could be bound in vitro by ACE2, which was purified from Vero E6 cells.[8]

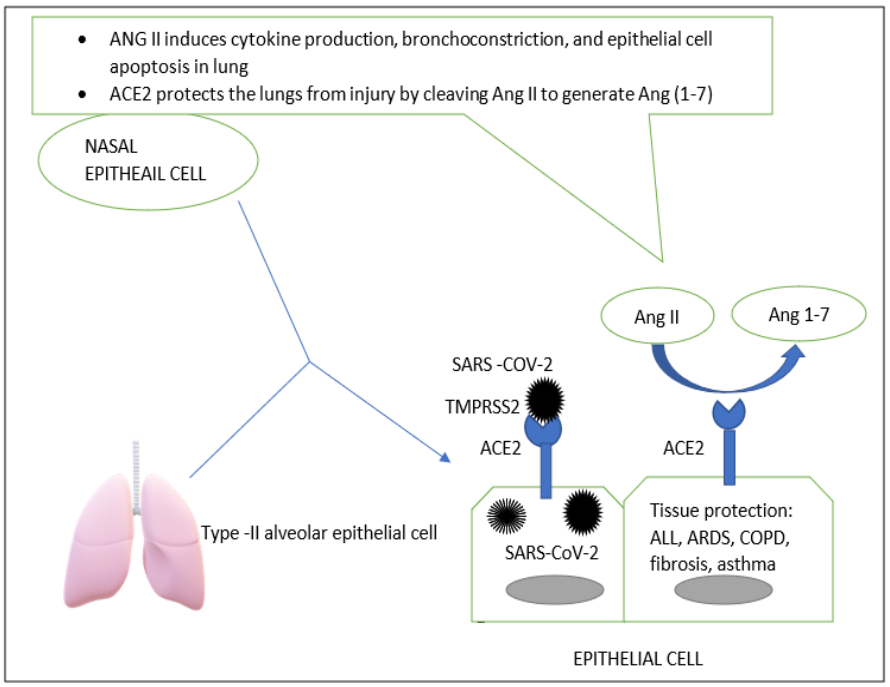

Figure 3: Expression of ACE2 in airway.

According to full-length genome sequencing, SARS-CoV-2 and SARS-CoV share 79.6% of the same sequence. 32 SARS-CoV-2 has been discovered using the ACE2 receptor for host cell entrance (Figure 3). Another participant, the

transmembrane protease TMPRSS2, a cellular serine protease that cleaves and activates the SARS-CoV-2 spike protein and enables human cell entry, is required to infiltrate the host cells.[34] A potential involvement for furin and furin-like proteases in SARS-CoV-2 cell entrance is suggested by the presence of a furin-like cleavage site in the spike protein of the virus.[33] By using cryo-electron microscopy, Wrapp et al. described the 3.5-angstrom-resolution structure of the SARS-CoV-2 trimeric spike protein. They discovered that the SARS-CoV-2 spike protein binds to ACE2 at least 10 times more tightly than the SARS-CoV-2 spike protein, which may help to explain why SARS-CoV-2 has a higher transmission efficiency than SARS-CoV-2.

The extracellular peptidase domain of ACE2 structurally recognizes the receptor binding domain of the SARS-CoV-2 surface spike protein mostly through the polar residues.[6]

2.2 ACE2 mediates SARS-CoV-2 infection

Viral infection begins with entry into host cells. Certain receptors on the membrane of host cells can bind to a spike glycoprotein on the coronavirus's viral envelope. It has been established from prior research that ACE2 is a particular functional receptor for SARS-CoV.[7] As evidence that ACE2 is the SARS-CoV-2 cell receptor, Zhou et al. demonstrated that SARS-CoV-2 may enter ACE2expressing cells but not cells lacking ACE2 or cells expressing other coronavirus receptors, such as aminopeptidase N and dipeptidyl peptidase 4 (DPP4).[7] Further research revealed that the SARS-CoV-2 spike glycoprotein has a 10- to 20-fold higher binding affinity to ACE2 than the SARS-CoV.

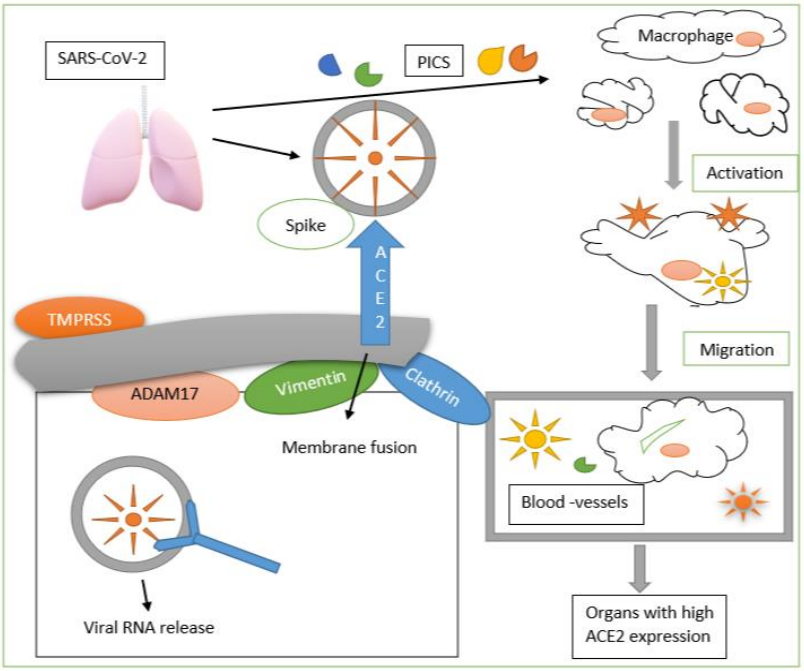

Figure 4: The process of SARS-CoV-2 entering host cells in the lungs and attacking other organs.

ACE2's subdomain I tip is where the spike glycoprotein's receptor-binding domain attaches. After binding, membrane fusion between the virus and the host cell is triggered, and subsequent release of viral RNA into the cytoplasm results in infection.[12] Infection with SARS-CoV causes internalization of the virus and intact ACE2 or its transmembrane domain. The spike glycoprotein does not obstruct the catalytically active site of ACE2, and binding occurs without regard to ACE2's ability to catalase peptides.[13] Several transmembrane proteinases and proteins, including vimentin

and clathrin, may be implicated in the binding and membrane fusion processes. Examples include transmembrane protease serine 2 (TMPRSS2), disintegrin and metallopeptidase domain 17 (ADAM17), and TNF-converting enzyme.[35] For instance, TMPRSS2 and ADAM17 both have the ability to cleave ACE2 in order to increase viral uptake and ectodomain shedding, respectively.[16] Nearly every human organ expresses ACE2 to variable degrees. The traditional immunohistochemical method and the more recent single-cell RNA sequence analysis of the respiratory system showed that ACE2 is primarily expressed on type II alveolar epithelial cells but only weakly expressed on the surface of epithelial cells in the oral, nasal, and nasopharynx mucosa and pharynx, suggesting that the lungs are the main target of SARS-CoV-2.[36] Moreover, ACE2 is widely expressed on the enterocytes of the small intestine, particularly in the ileum, as well as on the myocardial cells, proximal tubule cells of the kidney, and bladder urothelial cells. Via blood circulation, the cell-free and macrophage phagocytosis-associated virus may travel from the lungs to other organs with high ACE2 expression. For instance, quite a few COVID19 patients and up to 67% of SARS patients who experienced diarrhea displayed gastrointestinal symptoms. SARS-CoV-2 has been successfully isolated from fecal samples and has been reported to be actively replicating in small intestine enterocytes.[33]

3. PATHOPHYSIOLOG

3.1 Pathophysiology of coronavirus

Angiotensin-converting enzyme II (ACE2), the same receptor as SARS-CoV, is the route by which SARS-CoV-2 enters the host cell and may further elicit host immune responses based on prior knowledge of CoV. Genomic RNA is released by the SARS-CoV when it enters the cytoplasm and the host cell starts replicating. Double stranded RNA (dsRNA) can trigger an innate immune response by sensitizing TLR-3, which in turn triggers the generation of type 1 interferon (IFN) through signaling pathway cascades.[39] Important antiviral cytokines known as type 1 IFNs can activate the production of interferon-stimulated genes (ISGs).[24] On the other hand, the virus' spike protein (S protein) may be identified by TLR-4 and cause the MyD88-dependent signaling pathway to activate pro-inflammatory cytokines, drawing lymphocytes and leukocytes into the infection site. Antigen-presenting cells (APCs) transmit CoV antigens to T cells during adaptive immunological responses, which then to T cell differentiation and activation.[41]

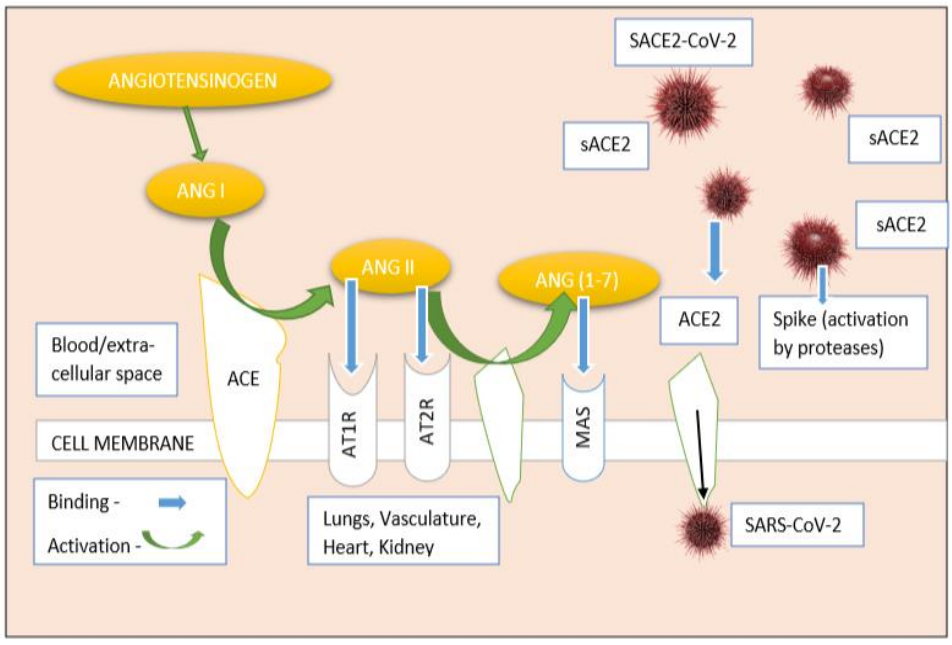

Figure 5: Entering of virus in host cell.

This procedure, which may be accompanied by a significant production of pro-inflammatory cytokines, is essential for the elimination of viruses but may also result in excessive inflammation.[28] Antiviral responses depend on coordination between the innate and adaptive immune systems. Innate immune responses are likely to be strengthened if adaptive immune responses fail to completely eradicate the virus, which could result in unmanageable inflammation. A possible cytokine storm mechanism is suggested by mounting evidence gathered from COVID-19 patients. This mechanism is based on an enhanced proinflammatory cytokine profile that, especially in severe patients, resembles a cytokine storm.[1]

In a study, researchers measured multiple cytokines in 41 COVID-19 patients and discovered that their levels of interleukin (IL)-1, IL-1R, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), IFN-, interferon-inducible protein (IP-10 [17]. Furthermore, it was observed that patients in ICUs had greater levels of IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1, and TNF- than patients in non-ICUs. Also, some studies have noted a notable increase in IL-6 levels, particularly in individuals who are suffering from severe conditions. Table1 lists the cytokines that have been reported to have changed in COVID-19 patients.[1]

According to a theory, people with severe COVID-19 have cytokine profiles similar to secondary hemophagocytic lymph histiocytosis (SHLH), which go hand in hand with rapidly progressing lung injury and multiorgan damage. Furthermore, in individuals with severe COVID-19, there are no obvious symptoms of immune system impairment, such as significant lymphopenia, spleen atrophy, or lymph node atrophy.[42]

Cytokine profiles reported in COVID-19 patient.[1]

Cytokines or chemokine	Changes in COVID-19
IL-1β	Increase in COVID-19 patients Undetectable in COVID-19 patients
L-1Rα	Increase in COVID-19 patients
IL-2	Increase in severe COVID-19 patients No significant change
IL-2R	Increase in severe COVID-19 patients
IL-4	Increase in severe COVID-19 patients No significant change
IL-6	Increase in severe COVID-19 patients Increase in COVID-19 patients, higher in severe patients
IL-7	Increase in COVID-19 patients, higher in severe patients
IL-8 (CXCL8)	Increase in COVID-19 patients Within normal range
IL-9	Increase in COVID-19 patients
IL-10	Increase in COVID-19 patients, higher in severe patients Increase in severe COVID-19 patients Within normal range
Basic FGF	Increase in COVID-19 patients
G-CSF	Increase in COVID-19 patients, higher in severe patients
GM-CSF	Increase in COVID-19 patients
IFNγ	Increase in COVID-19 patients No significant change

3.2 Asthma Pathophysiology

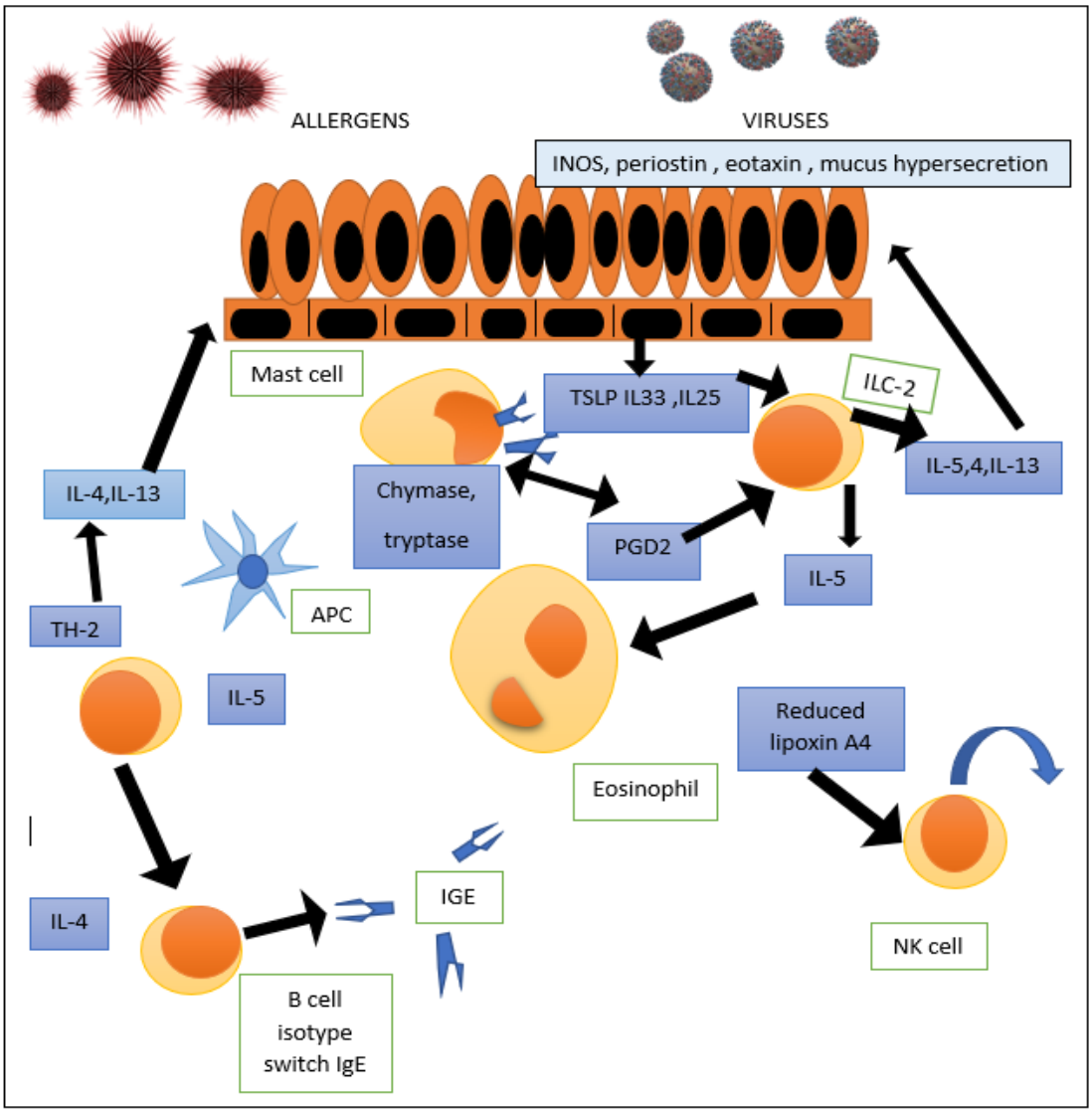

Figure 6: Pathophysiology of severe asthma.

Asthma is a common respiratory condition characterized by persistent airway inflammation, excessive mucus production, hyperresponsiveness, and remodeling. Type 2 immune responses typically mediate the majority of the disease. The type 2 immune response includes T helper (Th) 2 cells, type 2 B cells, group 2 innate lymphoid cells, type 2 macrophages, IL-4-secreting NK and NKT cells, basophils, eosinophils, and mast cells.[43] The regulatory network is influenced by a range of cytokines released by epithelial cells and the immune system.[17] For instance, IL-4 and IL-13 play crucial roles in the generation of allergen-specific immunoglobulin (Ig) E, the accumulation of Th2 cells and eosinophil in local tissues, as well as the control of the epithelial barrier, whereas IL-5, IL-9, and IL-13 contribute to eosinophilia and mucus production.[1]

4. COVID 19 IMMUNOPATHOGENESIS AND ASTHMA

The new pandemic COVID-19, brought on by the SARS-CoV-2 virus, has spread across the world.[1] Asthma and allergy sufferers are typically more likely to experience more serious consequences from virus infections.[20] Yet among other comorbidities and risk factors of the severe form of COVID-19, recent publications have amassed evidence

indicating the prevalence of allergic illnesses and asthma in individuals with COVID-19 is lower than expected.[19] First, coronavirus identification and infection depend on cellular receptors, namely the transmembrane protease serine 2 (TMPRSS2) enzyme that cleaves the docked spike protein of SARS-CoV-2 to allow for virus entry by membrane fusion. The genetic variations of the host and microbial infections affect the levels of ACE2 and TMPRSS2 gene expression. These levels are also controlled by innate immune responses, such as the production of interferons and mucins.[21] Age, gender, comorbidity, and type 2 allergic inflammation in asthma patients affect the expression of these two molecules in the respiratory epithelial cells after SARS-CoV-2 infection. Based on their patient cohorts, asthma and respiratory allergies are linked to decreased ACE2 expression in airway cells.[19] On the other hand, TMPRSS2 is a component of a network that secretes mucus and is mostly uncontrolled by type 2 allergic inflammation, primarily by interleukin-13. In the cells isolated from induced sputum, there was no difference in the expression of the ACE2 and TMPRSS2 genes between asthmatics and healthy individuals.[10]

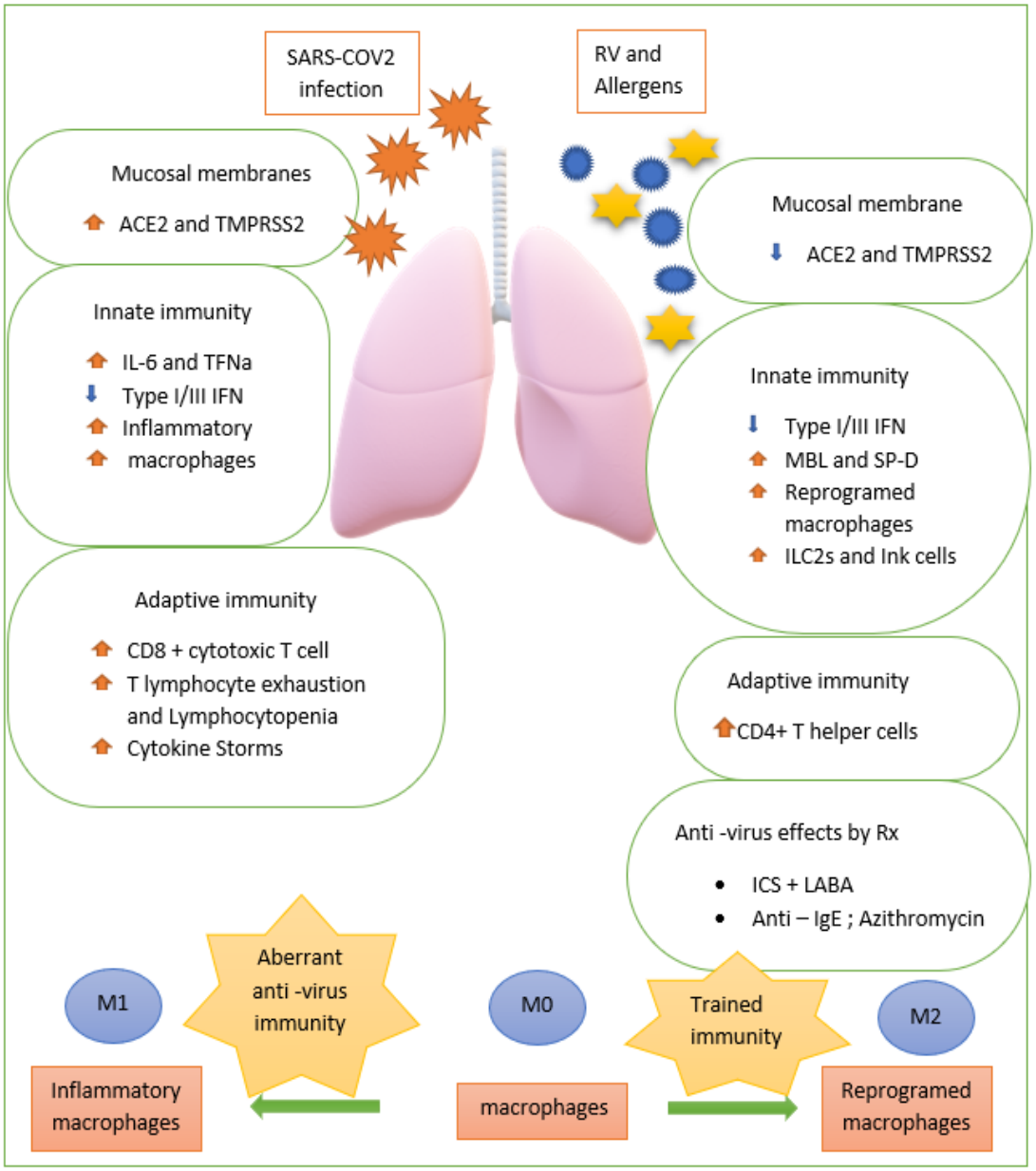

Figure 7: Immunopathogenesis of covid 19.

Second, the severity of ARDS and multiple organ failure in COVID-19-infected patients is determined by viral load and the host's immunological response. Due to decreased levels of IFN in their bronchial epithelial cells, asthmatic patients' innate immune response to COVID-19 infection may be compromised, but it may also be advantageous in lowering ACE2 expression, which depends on IFN synthesis.[29] In addition to IFNs, additional innate immunity molecules in the respiratory tract, such as mannose-binding lectin (MBL) and surfactant protein A (SP-A) and D (SP-D) generated by alveolar type 2 cells in the lung, which are also heavily infected by the SARS coronavirus, may also have antiviral activities.[22] These molecules, MBL and SP-D, have been found to bind spike protein of SARS coronavirus, inhibit its binding to the ACE2 cellular receptor, and are thereby capable of protecting the alveolar macrophages from virus-induced activation. These molecules are found in higher concentrations in the BALF of patients with asthma and respiratory allergies and are increased due to chronic inflammation.[23] Low levels of type I and type III interferon are the main cause of severe COVID-19. The idea that Decreased Innate Antiviral Defenses and Exuberant Proinflammatory Cytokine Production are the Defining and Driving Features of COVID-19 is supported by the juxtaposition of increased chemokine and high expression of IL-6.[37] The cytokine profile of asthmatics in response to SARSCoV-2 infection requires further research. Moreover, there is in vitro data to support ICS's preventive action against infections caused by coronaviruses. In fact, sputum research revealed that, particularly when large doses of ICS are administered, ACE2 expression levels in asthma patients using ICS are markedly lower than in those not taking ICS.[18] Current research suggests that asthmatics' myeloid cells and alveolar macrophages may have trained immunity that can give antiviral immunity in certain organs like the lungs. In vitro models have demonstrated that inhaled corticosteroids, either by itself or in conjunction with bronchodilators, inhibit coronavirus multiplication and cytokine generation.[38] Inhaled corticosteroids (ICS)-using asthmatics showed decreased expression of ACE2 and TMPRSS2 in their bronchial epithelial cells.[9] Despite the fact that this study lacked adequate controls, there is a clinical report of three COVID-19-infected patients' condition improving after utilizing inhaled ciclesonide.

Our results offer concrete proof that inhibiting IgE increases pDC IFN-response, which in turn increases pDC IgE response, reducing vulnerability to viral respiratory diseases.[40] What's more intriguing is that in a nonrandomized open-label clinical trial, azithromycin plus hydroxychloroquine significantly reduced viral load after six days of treatment compared to untreated controls in COVID19-infected patients.[10]

5. CONTROLLING ASTHMA DURING THE COVID 19 EPIDEMIC

Individuals with asthma who believe they may have COVID-19 have been given advice. The majority of advice is generic and is delivered to the broader public. Whether a cough is a symptom of COVID-19 or due to asthma is a concern for people with asthma. Asthma and COVID-19 symptoms may overlap in the early stages of the disease, with more distinct COVID-19 symptoms emerging only later.[3] If doubtful, it is advised that people with asthmatic cough contact healthcare professionals (HCPs). Individuals with asthma who have COVID-19 symptoms should continue to follow their asthma action plans, take their medications as prescribed, and call emergency services if they experience an asthma attack. It's important to let the first responders know that the person has COVID-19 symptoms.[4] An algorithm has been developed to help HCPs determine when a face-to-face evaluation is necessary (as opposed to a telemedicine evaluation) depending on the severity of the patient's asthma and the COVID-19 risk (high/low). Regarding HCP exposure, there is some information circulating (not sourced) that ambulance services are suggesting that crews should be at least 6 feet away and preferable in another room when evaluating peak expiratory flow rate (PEFR) in suspected COVID-19 in persons with asthma in their own homes. Strategies for aerosol medicine administration to lower the risk

of infection have been developed for hospitalized patients. In order to administer ward care, the British Thoracic Society recommends the Sharing Patient Assessments Cuts Exposure for Staff (SPACES) strategy, which is founded on the concept "maximum patient contact-minimum staff exposure.".[5]

5.1 A GUIDE FOR DIFFERENTIATING COVID 19 AND ASTHMA SYMPTOMS

- Healthcare professionals inform patients that because it is unusual to have fatigue, a high fever, or changes in taste or odor during an asthma episode, the presence of these symptoms is more likely to indicate COVID-19 infection.[26]
- In a joint statement, the Allergic Rhinitis and Its Impact on Asthma and the European Academy of Allergy and Clinical Immunology note that patients are finding it difficult to distinguish symptoms between asthma flare-ups and COVID-19 and that there is still a lack of clarity on this, which may lead people to put off seeking medical attention. They caution against doctors' propensity to 'just be safe' prescribe antibiotics to patients they feel are experiencing asthma exacerbations.
- Fever may assist distinguish between asthma exacerbations and COVID-19 in pediatric and adult populations, according to a recent report in the Journal of Pediatric. Nevertheless, caution should still be exercised as fever may also be present in asthma exacerbations brought on by other viruses. They point out that adult populations can better identify various symptoms that may assist distinguish between COVID-19 and asthma, such as myalgia, headaches that are confusing, pharyngitis, rhinorrhea, loss of taste and smell, diarrhea, nausea, and vomiting. They assert that travel history, close contact with a COVID19 infected person, and a child's lack of a history of atopic dermatitis may also aid in differentiating the two. Any child with asthma who exhibits a worsening cough or shortness of breath should have a COVID-19 screening.[5]

5.2 MANAGEMENT OF ASTHMA TREATMENT DURING COVID 19

Using asthma medication, such as inhaled corticosteroids and/or montelukast, as directed is the greatest method to prevent asthma exacerbations. So, during the COVID-19 outbreak, kids should continue taking their current asthma treatments. The CDC, the Global Initiative for Asthma, and the North American consensus guideline on allergy care during the COVID outbreak are just a few of the international organizations that support this suggestion [5]. Children should not reduce their dosage of any controller medication during this period unless "this is demonstrably favorable from an individual standpoint, with careful assessment of the balance between benefit and harm/burden."

Additional suggestions for keeping asthma under control include avoiding recognized asthma triggers including aeroallergens, frequently washing hands, physical separation and routine inhaler technique review.[44] If there was an aggravation, it "may require [children] to access the hospital system, where they would be more likely to come into contact with SARS-CoV-2 during the present pandemic.[25] Certain biologic medications, including omalizumab (anti-IgE) and mepolizumab (anti-IL5), are permitted for use in adolescents with moderate to severe asthma. The current advice is for teenagers who are taking these medications to keep doing so. The use of these drugs does not yet appear to raise the risk of COVID-19 infection or morbidity. In most cases, a metered dose inhaler or dry powder inhaler (turbuhaler or diskus) should be substituted for a child's nebulized asthma relief medicine. Nebulization increases the risk of viral lower lung deposition.[18] Additionally, because it triggers the cough reflex and produces "a high number of respiratory aerosols that may be propelled across a longer distance than is involved in a natural dispersion pattern," it raises the likelihood of infection transmission. There is a chance that nebulizer therapy in patients with COVID-19

infection can transmit potentially live coronavirus to susceptible bystander hosts, according to a recent editorial, which made the heartbreaking observation. During the COVID-19 epidemic, a child should only use a nebulizer at home if they have an inadequate response to a metered dosage inhaler/spacer, are unwilling or unable to follow the instructions for using a metered dose inhaler, or there are drug shortages (which are discussed in greater detail elsewhere in this article).[25]

6. CONCLUSIONS

In this context, the review attempts to highlight ACE2's involvement in COVID-19 disease, which contrasts with the vasoconstrictor and inflammatory effects of the latter. The lower expression of ACE2 and TMPRSS2 associated with asthma reduced COVID-19 morbidity and decreased susceptibility to SARS-CoV-2 infection. Infection with SARS-CoV-2 does not affect asthma patients differently in terms of biological or radiological state or clinical symptoms. Both individuals with and without asthma exhibited the risk variables for SARS-CoV-2 pneumonia that have been previously reported. This shows that the primary cause of the hospitalization was the COVID-19 infection. Moreover, unlike previous viral respiratory infections, SARSCoV-2 pneumonia did not appear to cause a substantial worsening of asthma. The best defense against COVID-19 during the pandemic is to maintain control of asthma. The use of biological agents and medications used to treat asthma, such as inhaler steroids (either alone or in combination), should continue.

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

1. REFERENCES

1. Shuang Liu, & Yuxiang Zhi1 & Sun Ying. “COVID-19 and Asthma: Reflection During the Pandemic”, Clinic Rev Allerg Immunol, 2020; 59: 78–88.
2. Brojakowska et al. “Clinical Implications of SARS-CoV-2 Interaction with Renin Angiotensin System”, 2020. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 24.
3. Beurnier A, Jutant E-M, Jevnikar M, et al. “Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalization”, 2020. Eur Respir J.
4. Nurhan SARIOĞLU. “Asthma and COVID-19: What do we know?”, Tuberk Toraks, 2020; 68(2): 141-147.
5. Jamie Hartmann- Boyce et al. “Asthma and COVID-19: review of evidence on risks and management considerations”, BMJ Evidence- Based Medicine, 2020.
6. YAO et Al. “Expression of ACE2 in airways: Implication for COVID-19 risk and disease management in patients with chronic inflammatory respiratory diseases”, Clin Exp Allergy, 2020; 001–12.
7. Sienko et al. “COVID-19: The Influence of ACE Genotype and ACE-I and ARBs on the Course of SARS-CoV-2 Infection in Elderly Patients”, 2020. Clinical Interventions in Aging, 2020; 15: 1231–1240.
8. Gheblawi et al. “Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System”, 2020. Circulation Research, 2020; 126: 14561474. DOI:10.1161/CIRCRESAHA.120.317015.

9. Michael Peters, Michael Montgomery, Mats W Johansson, Mario castro. “COVID-19 Related Genes in Sputum Cells in Asthma: Relationship to Demographic Features and Corticosteroids”, 2020. AJRCCM Articles Published 10.1164/rccm.202003-0821OC.
10. Tao-Te-Ching. “COVID-19 and asthma, the good or the bad?”, 2020. Allergy, 2020; 001–3.
11. Mário Morais-Almeid et al. “Asthma and the Coronavirus Disease 2019 Pandemic: A Literature Review”, 2020. Int Arch Allergy Immunol, 2020; 181: 680–688.
12. Liu et al. “Potential role of ACE2 in coronavirus disease 2019 (COVID-19) prevention and management”, Journal of Translational Internal Medicine, 2020; 8(1).
13. T. Behl, et al. “The dual impact of ACE2 in COVID-19 and ironical actions in geriatrics and pediatrics with possible therapeutic solutions”, 2020. Life Sciences, 257; 118075.
14. M. Adnan Shereen, S. Khan, A. Kazmi, N. Bashir, R. Siddique, “COVID-19 infection: origin, transmission, and characteristics of human coronaviruses”, J. Adv. Res, 2020.
15. N. Roshanravan, et al., “Angiotensin converting enzyme-2 as therapeutic target in COVID-19, Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14”, 637e639,
16. A. Heurich, et al., “TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein”, J. Virol, 88 (2013) 1293–1307, https://doi. org/10.1128/JVI.02202-13.
17. Jaclyn Quirt, Kyla j., Hildebrand Jorge Mazza, Francisco Noya and Harold Kim. “Asthma, allergy and Immunology”, 2020. https://www.ncbi.nih.gov/pmc/articles/PMC6157154/
18. https://www.ncbi.nih.gov/pmc/articles/PMC4166064/
19. https://www.statnews.com/2020/07/02/asthma-covid19-connection-research/
20. https://www.medpagetoday.com/infectiousdisease/covid19/86323
21. https://www.medscape.com/viewarticle/934133?src=mbl_msp_android&ref=share
22. https://www.medscape.com/viewarticle/929641?src=mbl_msp_android&ref=share
23. https://www.medscape.com/viewarticle/936363?src=mbl_msp_android&ref=share
24. CAMIOLO ET AL. “Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype”, 2020. J ALLERGY CLIN IMMUNOL.
25. Elissa M., MD, MPH, and Stanley J., Szefier, MD. “Managing Asthma During Coronavirus Disease- 2019: An Example For Other Chronic Conditions in children and Aldolescents”, 2020.
26. Dr Mark L Levy, Professor Alvaro Cruz Dr. “Asthma management during COVID-19 – guidance for healthcare professionals”, 2020; Z4-24127.
27. Wil Lieberman-cribbin, MPH, Joseph Rapp, MPH, Naomi Alpert, MS, Stephanie Tuminello, MPH, Emanuela Taioli, MD, PhD, New York, Ny. “The Impact of Asthma on Mortality in patient with COVID-19”, 2020.
2. https://journal.chestnet.org/article/S0012- 3692(20)31645-7/fulltext.
28. Peters, Sajuthi, Deford, et al. “COVID-19–related Genes in Sputum Cells in Asthma”, American Journal of Respiratory and Critical Care Medicine, 2020; 202(1).
29. Tania Maes, Ph.D, Ken Bracke, Ph.D, Guy G. Brusselle, Ph.D, M.D. “COVID-19, Asthma, and Inhaled Corticosteroids: Another Beneficial Effect of Inhaled Corticosteroids?”, American Journal of Respiratory and Critical Care Medicine, 2020; 202(1).

30. Daniel Jackson, Meyer Kattan, Robert A Wood. “Association of Respiratory Allergy, Asthma and Expression of the SARS-CoV-2 Receptor, ACE2”, 2020. Journal of Allergy and Clinical Immunology.
31. Carly G.K. et al. “SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues”, 2020. Elsevier Inc.
32. José Luis Izquierdo et al. “The impact of Covid-19 on Patients with Asthma: A big data analysis”.
33. Koichi Yuki, Miho Fujiogi, Sophia Koutsogiannaki. “COVID-19 pathophysiology: A review”, Clinical Immunology, 2020; 215; 108427.
34. Rios CL, et al. “Type 2 and interferon inflammation strongly regulate SARS-CoV-2 related gene expression in the airway epithelium” [published online ahead of print April 10, 2020]. bioRxiv.
35. Li C, et al. “Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage” [published online ahead of print February 12, 2020]. medRxiv.
36. Wood RA, et al. “Association of respiratory allergy, asthma and expression of the SARSCoV-2 receptor, ACE2” [published online ahead of print April 22, 2020]. J Allergy Clin Immunol.
37. Zhou Y, et al. “Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan” [April 12, 2020]. J Allergy Clin Immunol.
38. Roswit WT, et al. “IL-13induced airway mucus production is attenuated by MAPK13 inhibition”. The Journal of clinical investigation, 2012; 122(12): 4555-68.
39. Bermudez-Gonzalez, M., et al., “A serological assay to detect SARS-CoV-2 seroconversion in humans”. medRxiv, 2020.2003.2017.20037713. 10.1101/2020.03.17.20037713.
40. Blanco-Melo et al., “SARS-CoV-2 launches a unique transcriptional signature from in vitro, ex vivo, and in vivo systems”. bioRxiv, 2020.2003.2024.004655 REFERENCE Page 26.
41. Fan Y, Zhao K, Shi ZL, Zhou P (March 2019). "Bat Coronaviruses in China" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC646618.
42. Almeida JD et al. (November 1968). "Virology: Coronaviruses"
43. Sturman LS, Holmes KV (1983-01-01). Lauffer MA, Maramorosch K (eds.). "The molecular biology of coronaviruses"
44. Lalchhandama K. "The chronicles of coronaviruses: the bronchitis, the hepatitis and the common cold", 2020.