Coronavirus and Its effect on the respiratory system: Is there any association between pneumonia and immune cells

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ABSTRACT

Background: With a new mutation, coronavirus has now become an important pandemic that gripped the entire world. Coronavirus infection often begins in the nasopharynx and destroys the olfactory epithelium. Despite many studies, little progress has been made in the treatment of coronavirus. This study aimed to further investigate the pathogenicity of coronavirus to reduce its infection by examining the virus function in the body and its stages of infection. Material and Methods: With the aim of investigating the coronavirus and its effect on the human respiratory system from 1992 to 2020, this study examined the coronavirus and its different aspects and tried to answer whether there is an association between pneumonia and immune cells. This study was conducted in April 2020 and to obtain the related papers on the characteristics of the virus, Nature, ISC Pubmed, Medline WHO, NCBI, and PsycINFO databases were used. Out of 284 papers, 53 were used in this study. Result: Studies have shown that avoiding infected areas and strengthening the immune system inhibit the virus to bind the mucosal layers. Given the important role of acquired immunity and lymphocytes against coronavirus, it is necessary to pay attention to boost the immune system in adults and the elderly. Antioxidants help reduce the oxidative stress and inflammation in the immune system thus help it regenerate better. The results showed that children are susceptible to the virus though have lower mortality and clinical manifestations than adults. Conclusion: The vaccine should receive further attention and in the long run, antiviral drugs and broad-spectrum vaccines are produced for infectious diseases.

Keywords: Coronavirus, COVID-19, immune system, pneumonia, respiratory system

Introduction

A simple cold can be caused by an infectious virus entering the upper respiratory tract, including the nose. In the meantime, the throat, larynx, and sinuses may also be involved, with symptoms such as cough, sore throat, runny nose, sneezing, headache, and fever. However, the symptoms of COVID-19, which results from the novel coronavirus, can overlap with the symptoms of colds, allergies, and flu. Like other types of colds, the virus colonized first in the nose. Coronavirus are a group of viruses¹ that can cause diseases ranging from mild colds to more severe diseases such as severe acute respiratory syndrome and COVID-19. COVID-19 has symptoms similar to those of colds and flu, except that it primarily affects the lungs and usually causes fever, dry cough, and shortness of breath.² Later identified as the new coronavirus pneumonia (NCP), pneumonia caused by the novel coronavirus was spread in Wuhan, China in December 2019 as a highly contagious disease with clinical features very similar to those of pneumonia. The World Health Organization (WHO) has declared its outbreak a “global public health emergency.”
Coronaviruses are highly species specific. The pathogenesis of their disease in human is not well understood. Most animal coronaviruses tend to epithelial cells in the respiratory and gastrointestinal tract of animals. Coronavirus infections in human is usually limited to the upper respiratory tract.

The 2003 SARS outbreak was identified by a serious respiratory illnesses, including pneumonia and progressive respiratory failure. The virus appeared to have originated from a non-human host and has acquired the ability to infect human.

Materials and Methods

With the aim of investigating the coronavirus and its effect on the human respiratory system from 1992 to 2020, this study examined the coronavirus and its different aspects and tried to answer whether there is any association between pneumonia and immune cells. This study was conducted in April 2020 and to obtain the related papers on the characteristics of the virus, Nature, ISC Pubmed, Medline WHO, NCBI, and PsyINFO databases were used. The study was conducted by examining aspects and issues related to the Coronavirus family, its attachment, replication cycle, life cycle, medical treatment, pathogenesis in different populations, and clinical trials. The keywords were also searched in the databases to collect information on the coronavirus, including respiratory disease, coronavirus, COVID-19, immune system, coronavirus prevalence, pneumonia outbreak, etc., out of 284 papers, 53 were used in this study.

Coronavirus family

Coronaviruses are the positive-sense single-stranded enveloped RNA viruses of the nidovirales order. Under an electron microscope, they are almost spherical or relatively plumiform. As one of the largest RNA viruses, the size of the coronavirus genome is between 26 and 32 kb. The coronavirus RNA genome has a methylene cap 5' and a polyadenylated tail 3'. The key function of coronavirus RNA synthesis is encoded by the replicase gene. The gene is made up of more than 20,000 nucleotides, encoding two polyproteins, pp1a and pp1ab, and is processed by viral proteases. 7 Coronavirus families are phenotypically and serologically divided into 4 types: alpha, beta, gamma, and delta. There are approximately 3 types of coronaviruses in humans, mammals, and birds. Human coronaviruses are caused by two types of alpha and beta. The first open reading frame (ORF), which encodes almost 67% of the entire genome, includes 16 non-structural proteins (NSPs), while the remaining frames encode other structural proteins. Coronaviruses have four types of proteins: The spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, among which the S protein attached to the virus membrane plays an important role in attaching and entering to the host cell. The different types of human coronavirus include (1) human coronavirus 229 (HCoV-229E); (2) human coronavirus OC43 (HCoV-OC43); (3) Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV); (4) human coronavirus NL63 (HCoV-NL63); (5) human coronavirus HKU1; (6) Middle East Respiratory Syndrome Coronavirus, formerly known as novel human coronavirus-2012 or HCoV-EMC (MERS-CoV); and (7) Severe Acute Respiratory Syndrome 2 (SARS-CoV-2), formerly known as 2019-coronavirus or 2019-novel coronavirus (2019-nCoV). The HCoV-229E, -NL63, -OC43, and -HKU1 viruses regularly infect the human population and cause respiratory infections in children and adults. The SARS-COV-2 belongs to the beta-coronavirus group. COVID-19 is the third known coronavirus disease of animal origin after SARS and MERS syndrome, both of which belong to the beta coronavirus. Figure 1.

Coronavirus virus replication cycle

The coronavirus attaches to the receptors on the surface cells of the host cell through viral glycoprotein attachments. Some coronaviruses attach to sialic acid glycoproteins and glycolipids through receptors and/or hemagglutinin esterase glycoproteins. Interactions between coronavirus and host cell receptors determine the level of specialization, tissue degeneration, and pathogenicity of the virus. Coronavirus infection begins by attachment of subunit S1 of protein S to its specific receptor. This alters the structure of the S2 subunit of the S protein, which facilitates the attachment of the virus and the plasma membrane of the cell. Following the release of nucleocapsids into the cytoplasm, the viral gRNA is translated by ribosomal frameshift to produce pp 1a and pp 1ab polyproteins. Pp 1a and pp 1ab are self-proteolytically processed by viral and host proteases to form 16 non-structural proteins (NSPs), which are then assembled to form polymerase-replicase. Polymerase-replicase participates in the replication of coronavirus, a process in which genomic RNA is replicated and transgenic RNAs are transcribed and translated to create structural proteins. The viral products synthesized are collected at ERGIC and sprouted out of the plasma membrane as a smooth-walled vesicle to exit through exocytosis. Host factors that facilitate or inhibit infection were shown in green and red, respectively. APN, aminopeptidase N, ACE2, angiotensin

Figure 1: Corona virus structure (15)
2 converting enzyme, DPP4, diptidyl peptidase 4 9-O-Ac sialic acid, 9-O acetylated sialic acid, IFITM, interferon-induced membrane protein, ATPase, ATP1A1, sodium-Potassium transport, alpha-1 polypeptidase, HnRNP A1, heterogeneous ribonucleocytotprotein A1, MADP1, CCHC-type zinc finger, RNA-binding motif 1, DDX1, ATP-dependent helicase RNA, PCBP, PABP, Poly r (C)-binding protein; COPB2, Coatomer protein complex, subunit 2 beta (beta-prime); GAPDH, Glycerol-3-phosphate dehydrogenase; ERGIC, VCP, Valvyn protein. Coronavirus is an intracellular parasite that uses host cell organs to multiply and expand. The interaction of the virus and the host cell is the basis of the disease. Figure 2 shows the virus attachment, entry into the host cell, translation, simulation, transcription, genome replication, the mRNA transcription, assembly, and the sprout of the newly closed virus.\footnote{[17]}

The virus destroys the cell wall after binding and inserts its genome into the host cells.\footnote{[17]}

**Coronavirus attachment**

Coronavirus infection begins by attachment of subunit S1 of protein S to its specific receptor. The host receptor is the main determinant of pathogenesis. S protein is composed of two domains, S1 and S2. Interaction between S1 domain and the receptor deforms the S protein, which causes the virus membrane and host cell to be fused through the S2 domain. The main receptors of the host cells in human coronaviruses of amino peptidase N with HCoV-229E,\footnote{[18]} angiotensin-converting enzyme 2 (ACE2) by SARS-CoV\footnote{[19]} and HCoV-NL63,\footnote{[20]} dipeptidyl peptidase 4 (DPP4) by MERS-CoV and 9-O-sialic acid are identified by HCoV-OC43 and HCoV-HKU1.\footnote{[21]} Apart from the common endosomal pathway, some CoVs may also enter the cell through a non-endosome pathway or a combination of both. Low pH in the cellular environment and endosomal cathepsins of the cysteine protease may facilitate membrane fusion.\footnote{[22]} Recent evidences support the role of cathepsin L in the entry of SARS-CoV and MERS-CoV.\footnote{[23]} Other host proteases, such as the membrane-anchored serine protease (TMPRSS2) and a trypsin-like protease TPRSS11D can alter the S domain.\footnote{[24]} Many host cells also have their own specific factors to limit virus entry. Using cell culture, family of interferon inducible transmembrane proteins (IFITM) have been identified, which can circulate HCoV-229E and HCoV-NL63 S proteins in the bloodstream, as well as prevent highly pathogenic SARS-CoV and MERS proteins.\footnote{[25]}

**Coronavirus lifespan**

At different surfaces, the virus can survive from 2 hours to 9 days. At higher temperatures, such as 30 to 40°C, its persistence considerably decreases. Decreased virus lifespan at temperatures above 30°C has been confirmed for the SARS virus. The SARS is genetically one of the most similar viruses to the novel coronavirus. A temperature of 4°C can increase the survival of coronavirus for up to 28 days. However, the amount of the virus on the surface is effective in its persistence so that when there was a low amount of the virus on a surface, its persistence would been significantly decreased. Higher humidity also makes the virus more persistent; the virus survival is significantly higher at 50% moisture than in 30% moisture.\footnote{[18]}

**Pulmonary and respiratory injuries**

Because of the pathogenicity of the virus, which is very similar to that of SARS in severe cases, coronavirus has a strong negative effect on the respiratory system. Most people with
COVID-19 have only mild or no side effects, with an average of 14% of severe illnesses requiring hospitalization and oxygen support, and 5% requiring hospitalization. In severe cases, COVID-19 can be associated with acute respiratory distress syndrome (ARDS), sepsis, and septic shock, acute renal failure, and heart failure. Old age and chronic diseases have been reported as risk factors for mortality. Recent multivariate analysis of old age has confirmed a high score in the sequential organic failure assessment (SOFA) and have been associated with high mortality. Among the elderly, the number of people in need of hospitalization and respiratory support has sharply increased, and the mortality rate in the elderly over 80 years has been reported to be approximately 21 due to severe pneumonia. In most cases, the disease occurs as a fever or without any respiratory symptoms; however, due to damage to the lung tissue, various degrees of pulmonary abnormalities later appear in all patients. These cases have been observed in lung scan imaging.

**Immune system and its function**

The human immune system is a complex network of specialized cells, tissues, and organs that is responsible for protecting humans against diseases caused by certain pathogens such as viruses, bacteria, and other parasites. This system stops the spread of infection in the body, identifies the intrinsic cells from the non-intrinsic ones, and eliminates the infected cells. The immune system is divided into two parts: innate immunity and acquired immunity. Intrinsic immunity, the first line of defense against pathogens, includes physical barriers in the skin and mucous membranes that prevent or limit infection by most pathogenic microorganisms. On the other hand, acquired immunity specifically identifies the invasive and infected cells. To be successful, the immune system produces a large number of cells. Most of these cells are produced in the bone marrow after early childhood. In acquired immunity, T and B cells create adaptive immunity and act on cancer and fight viruses. In the intrinsic immunity, neutrophils have the phagocytosis role and local killing, while monocytes are the primary response and responsible for phagocytosis and antigen production. The adult species in the tissues are called macrophages. Basophils and eosinophils act against parasites; however, they play an important role in killing pathogens in the viral infection of T lymphocytes.

One of the most important functions of the lymphocytes is the identification of antigens. The specificity of the acquired immune system is that viral antigens are exposed to T lymphocytes by antigen-presenting cells. Antigen presenting cells include endothelial cells, macrophages, and dendritic cells. By binding to receptors or antigens on the surface of the virus and digesting the antigens inside them, B lymphocytes transcribe a large number of copies and provide them for T lymphocytes. T lymphocytes transcribe these antigens and specifically play a role in eliminating the virus by providing surface-binding receptors specific to the virus.

Studies showed that with increased age, immunity decreases in most cases in patients with coronavirus. In adults, CRP protein increases with infection and T lymphocytes decrease. It is while in children, CRP protein increases slightly and T lymphocytes greatly increase, which reduces the symptoms in children.

**The association of pneumonia and immune cells**

Initiating an immune response against the invasive microorganisms such as the viruses requires the host immune system to identify the pathogen through its structure. Antigenic structures are detected in virus-infected cells by pattern recognition receptors. There are several types of known PRRs, including Toll-like receptors (TLR), RIG-I-like receptors (RLR), NOD-like receptors (NLR), C-type lectin-like receptors (CLL), and cytoplasmic DNA receptor such as cGAS, IFI16, STING, and DAI. After detecting virus compounds, PRRs initiate appropriate and effective antiviral responses, which include the production of a variety of cytokines and adaptive and inflammatory immunity responses. Interferons are key cytokines produced after virus infection that induce the initiation of the immune response and subsequent adaptation.

After binding and digesting the antigenic parts of the coronavirus, macrophages present the parts of the CoV antigen to the T lymphocyte cells. This process leads to the activation and detection of T cells and the production of cytokines associated with various subsets of T cells (e.g., 17Th), followed by the widespread release of cytokines to enhance the immune response. However, in many cases, in patients with weaker immune systems, the number of T lymphocytes decreases due to the lack of accurate identification of the virus, cytokines are produced in large quantities, and the inflammatory response increases. Continued production of inflammatory mediators due to virus stability has a negative effect on NK and CD8 T cell activation. Nevertheless, CD8 T cells produce very effective mediators for clearing CoV.

Studies on coronavirus have shown that the production of interferons is important for increasing the release of antiviral proteins. However, CoV non-structural proteins during pulmonary pneumonia may interfere with TLR-3 signaling and prevent TLR-3 activation and immune response. TLR-4 is likely to detect the S protein and lead to the activation of pre-inflammatory cytokines through the MyD88-dependent signaling pathway. The virus-cell interaction leads to severe production of immune mediators. The secretion of large amounts of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) increases in response to CoV infection in infected cells. These chemokines and cytokines absorb lymphocytes and leukocytes to the site of infection. In people with weaker immune systems and middle-aged people, an innate response such as fever, inflammatory mediators, etc., is more common. Increased cytokines disrupt airways and increase the severity of pneumonia. In people with stronger immune system, T lymphocytes act more quickly and specifically eliminate the pathogen. There has also been a sharp decrease in the number of
T cells in patients with the SARS, which is genetically very similar to the novel.[26,43-48] This indicates the major role of lymphocytes in specific immunity, and the relation between pneumonia and immune cells can be seen in the type of immune cells.

**Pharmacological and non-pharmacological treatment**

There is currently no definitive antiviral or vaccine treatment for coronavirus infections, and efforts to develop effective drugs have been made since the virus began to spread.[19] The production of safe and stable vaccines is a major challenge. On the other hand, research and production of new drugs is a very long process. In such a sudden epidemic, scientists were unable to produce new drugs by following molecular biology strategies. So, there was another option: a regular screening of available drugs to see if they have an effect on coronavirus (Drug repositioning).[27] The FDA-approved antiviral drugs including penciclovir nitrazine, nalfamusta, and Chloroquine, and two antiviral drugs with a wide range of redexivir and faviriv have been evaluated on the cytotoxicity of virus performance and the infection of the novel coronavirus 2019. Chloroquine is well described in vitro in uncoating inhibition and post-translational modification in newly synthesized proteins, particularly glycosylation inhibition in many viruses, including HIV. Other clinical trials have shown that remidesir is a promising antiviral drug against multiple RNA viruses (coronavirus, SARS, and MERS) in cultured cells and in mice and non-human (NHP) cells.[16] HIV antiviral drugs (Anti-Retroviral Therapy) have also been entered into human studies. ART drugs stop the progression of AIDS by inhibiting the enzyme involved in virus replication. However, Lopinavir has been shown to inhibit coronaviruses such as SARS and MERS and possibly novel coronavirus.[17] Currently, the best way to fight COVID-19 is to control the sources of infection. Strategies include early detection, reporting, isolation and quarantine, supportive therapies. Timely dissemination of epidemic information and maintaining social order is also very useful. Protective measures, including promoting personal hygiene, wearing medical masks, adequate rest, and proper ventilation of rooms can effectively prevent coronavirus infection.[18] In addition, antioxidant- and herbal-based treatments have been used in many patients with pneumonia to reduce the severity of the disease.[14,19]

**Prevention of the disease**

The best way to prevent infection is to avoid exposure to the virus, especially in poorly ventilated areas. However, with preventive health measures such as hand washing, avoid contacting sick people, using a home moisturizer, avoid touching the eyes, nose, and mouth, drinking plenty of fluids can prevent the spread of respiratory viruses such as COVID-19.[16,51] To avoid attending infected areas is also one of the best ways to prevent the disease. Viruses are transmitted in crowded environments in the form of bonded particles. Virus volume plays an important role in the severity of the respiratory diseases. Viruses must be bound to the cellular receptor for infection; at a very low volume, the possibility of binding is greatly reduced, and this is highly important in the infection.[22,23]

Strengthening the immune system is another important factor in preventing and improving the disease. Immune system before infection could kill viruses in the first place. For example, the secretion of lysozyme in the eyes is one of the most important enzymes in destroying the walls of bacteria and viruses, and the secretion of mucus in the layers of epithelial cells plays an important role in the non-proliferation of viruses. Also, after getting the virus, boosting the immune system helps to heal and reduce the severity of the disease.[34-38]

**Conclusion**

Studies have shown that avoiding infected areas and strengthening the immune system inhibit the virus to bind the mucosal layers. Given the important role of acquired immunity and lymphocytes against coronavirus, it is necessary to pay attention to boost immune system in adults and elderly. Antioxidants help reduce the oxidative stress and inflammation in the immune system thus help it regenerate better. The results showed that children are susceptible to the virus though have a lower mortality and clinical manifestations than adults.

Another important issue was the virus volume entering the body, which should be investigated so its effect on the severity of the disease. Also, the vaccine should receive further attention and in the long run, antiviral drugs and broad-spectrum vaccines be produced for infectious diseases. It is recommended that despite the centrality of the immune system in the severity of the disease, a study be performed on patients with coronavirus with the aim of determining the effects of different types of plant extracts on these patients and then examining immune system cells.

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**Conflicts of interest**

There are no conflicts of interest.

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