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Article Review

Human immune response to SARS-CoV-2 infection

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HIGHLIGHTS

- The SARS-CoV-2 infection causes innate and adaptive immune responses
- SARS-CoV-2 RNA mutations result in impaired immune system work

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A B S T R A C T

COVID-19 is an acute respiratory infection caused by a new type of Coronavirus, SARS-CoV-2, which first appeared in Wuhan, China in December 2019. COVID-19 then became a pandemic in various countries in early 2020. In this article it contains review that discusses the immune response in humans due to SARS-CoV-2 infection, using the narrative literature review method, a total of 36 articles (6 from Elsevier, 24 from PMC, and six from Springer). It is known that the pathogenesis of COVID-19 and the manufacture of drugs and vaccines are still under investigation, but in infected patients, innate immune responses in the form of alveolar macrophages, dendritic cells, airway epithelial cells, congenital lymphocytes, and neutrophils work together in the fight against infection. Next comes the adaptive immune response in the form of antibodies (immunoglobulins) which help in fighting infections due to SARS-CoV-2. These immune responses include increasing levels of cytokines, coagulation parameters, C-reactive protein, neutrophils, and decreasing total lymphocytes. It is also known that COVID-19 patients with severe disease often experience higher total antibody, IgM responses, and IgG responses than COVID-19 patients without the congenital disease. IgG antibodies are present in the serum, so the serum in COVID-19 patients who have recovered can be used for therapy in COVID-19 patients who have not healed, as long as the drug and vaccine are under investigation.

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1. INTRODUCTION

The disease called coronavirus disease 2019 (COVID-19) has become an epidemic in Wuhan City, Hubei Province, China, in December 2019. COVID-19 is caused by severe acute respiratory Coronavirus two syndromes (SARS-CoV-2), previously known as 2019-nCoV.[1]

SARS-CoV-2 became a pandemic in various countries until early 2020.[2] The virus was named SARS-CoV-2 because it has genetic similarities with SARS-CoV of the genus Betacoronavirus which was an epidemic in 2002-2003.[3,4]

On April 30, 2020, WHO stated globally 3,090,445 positive cases were confirmed to be COVID-19 with 217,769 deaths.[5] While in Indonesia, as of May 08, 2020, there were 13,112 confirmed positive cases of COVID-19, with 2,494 victims recovered, and 943 victims died.[6] In Indonesia, it's also known that COVID-19 fatality rate is quite high in five provinces, namely Banten (11.1%), East Java (10.7%), DKI Jakarta (8.6%), Central Java (7%), and West Java (6.6%). In addition to these provinces, there are five provinces that report the highest cure rates, namely Riau Islands, Bali, Aceh, Gorontalo, and DI Yogyakarta.[7]

SARS-CoV-2 infects humans thought to have originated from bats sold in the largest seafood market in Wuhan.[1] Infected humans can transmit the SARS-CoV-2 virus through sparks from the nose or mouth when coughing, sneezing, and or when breathing.[8] These splashes can fall on nearby objects or surfaces, and people who touch the object or surface and then touch their eyes, nose or mouth can also be infected with SARS-CoV-2 because the virus from the hands moves and enters the lungs.[8,9]

SARS-CoV-2 infection can cause mild, moderate or severe symptoms.[10] The main clinical symptoms are fever >38 ° C, dry cough, and difficulty breathing.[11] In some cases, even to experience heavy congestion, severe fatigue, muscle aches, and diarrhoea.[12] Some patients experience shortness of breath for one week with severe cases such as acute respiratory distress syndrome (ARDS), shock, septic, metabolic acidosis, and bleeding.[10,12]

SARS-CoV-2 is an RNA virus that has a spike glycoprotein (protein S) that can bind to the angiotensin-converting enzyme 2 (ACE2) receptor.[13] The S protein enters the host cell by attaching and binding to the ACE2 receptor, so the receptor-binding domain (RBD) of the S protein automatically recognizes that the receptor belongs to the host.[14] This can eventually combine the virus with the host membrane, and then the virus antigen will be exposed to the antigen presentation cell (APC).[15] ACE2 in the lungs is found in type 2 alveolar cells,[16] this is what causes in the case of COVID 19 symptoms such as peneumonia.[7]

The pathogenesis of COVID-19 and the manufacture of drugs and vaccines are still under investigation. For most patients, COVID-19 can only affect the lungs because most are respiratory diseases, with the main mode of infection being human-to-human transmission through direct contact from infected individuals through coughing or sneezing. COVID-19 has a possible asymptomatic incubation period of 2-14 days during which the virus can be transmitted.[12] When the virus infects, the antigen will be recognized by the immune system, so that an immune response is formed. To find out the immune response formed, the researchers conducted a review of various journals related to SARS-CoV-2 and the immune response in the human body.

2. REVIEW METHOD

The review method used in this article is a narrative review, which is a way to review existing literature and lean to the qualitative interpretation of prior knowledge, by summarizing or synthesizing what has been written on a particular topic but not looking for generalizations or cumulative knowledge from what is reviewed.[17] Articles were searched for keywords COVID-19 and SARS-CoV-2. 19.940 articles were obtained (849 from Elsevier, 9,547 from PMC, and 830 from Springer). The inclusion criteria we used were articles that discussed human immune responses to SARS-CoV-2 infection (based on previous SARS-CoV infections), which were fully accessible. From these criteria, 36 articles were obtained (6 from Elsevier, 24 from PMC, and 6 from Springer). The articles used are articles published in 2002-2020. This article discusses how SARS-CoV-2 infects host cells, and the human immune response infected with SARS-CoV-2. The data obtained is then described and supported by relevant references obtained from credible sources.

3. RESULTS AND DISCUSSION

How to SARS-COV-2 infect a human (Based on SARS-COV)

SARS-CoV-2 is a new Coronavirus subfamily that belongs to the β-coronavirus family which has 79.5% genetic similarity with SARS-CoV, the causative agent of the epidemic in 2002-2003.[18] SARS-CoV-2 has a genome structure like Coronavirus in general, which includes RNA viruses with particle sizes of 120-160 nm.[15] SARS-CoV-2 is thought to originate from bats which then mutate and infect humans. SARS-CoV-2 is closely related to Coronavirus in bats (Bat-SL-CoV ZC45 2018) and also Coronavirus in pangolins (Pangolin-CoV GX-P5E 2017).[7] There are no significant differences in the SARS-CoV-2 glycoprotein spike gene sequence found in Indonesia and the Wuhan-Hu-1 isolate from China.[19] SARS-CoV-2 has 96.2% genetic similarity with bat Coronavirus,[1] and have a 91% genome similarity to the anteater Coronavirus.[15] The structure of SASR-CoV-2 also has similarities with other SARS viruses.[20] The body structure of SARS-CoV-2 is presented in figure 1.

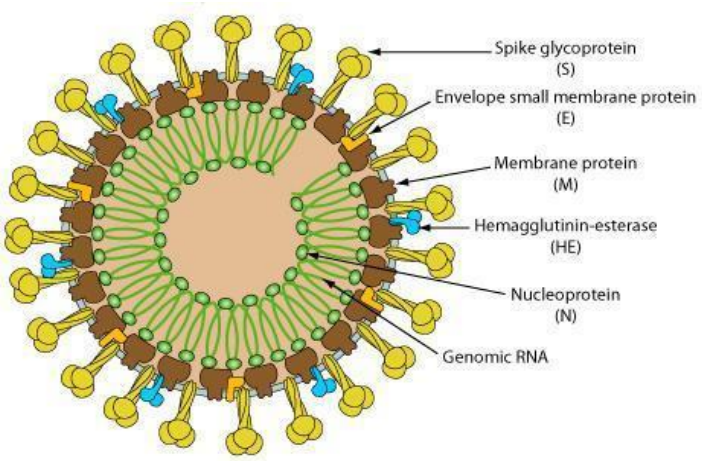

Figure 1. SARS-CoV-2 Body Structure[3]

The structure of SARS-CoV-2 consists of spike glycoprotein (protein S), protein envelope (E), membrane protein (M), hemagglutinin-esterase (HE), nucleocapsid (N), and genomic RNA. S protein is the only viral protein responsible for the entry of the virus into the host cell,[21] S protein protrudes from the virion envelope and plays an important role in attaching the body of the virus to the host receptor.[22,23] Protein E is the smallest protein that is abundantly expressed in infected cells, where it participates in the assembly and development of CoV.[24] M protein is the most abundant protein and forms E protein, M protein is directly related to nucleocapsid and together encourages the formation of protein E in viruses.[24] Hemagglutinin-esterase (HE) is a part of protein E which acts as a lectin and is a receptor-destroying enzyme.[25] The nucleocapsid (N) is seen as a ribonucleoparticle (RNP) because its components correspond to the RNA genome, which is coated by a nucleocapsid protein molecule. Nucleocapsid proteins interact with the RNA genome and coat the genome extensively.[26] RNA genome is the genetic material in the form of a ribonucleic acid single strand (ssRNA) or double-strand (dsRNA) that functions as a store of genetic information and can replicate.[27] In SARS-CoV-2 RNA that is owned is single-stranded RNA (ssRNA).[28]

SARS-CoV-2 has similarities with SARS-CoV which requires specific cellular receptors to infect host cells, namely, angiotensin-converting enzyme 2 (ACE2).[29] ACE2 is a receptor in the form of a central enzyme in the renin-angiotensin system, which negatively regulates the renin-angiotensin system by deactivating Angiotensin II.[30] ACE2 attaches to the outer surface (membrane) of cells in several organs such as the lungs, arteries, heart, kidneys, and intestines.[31]

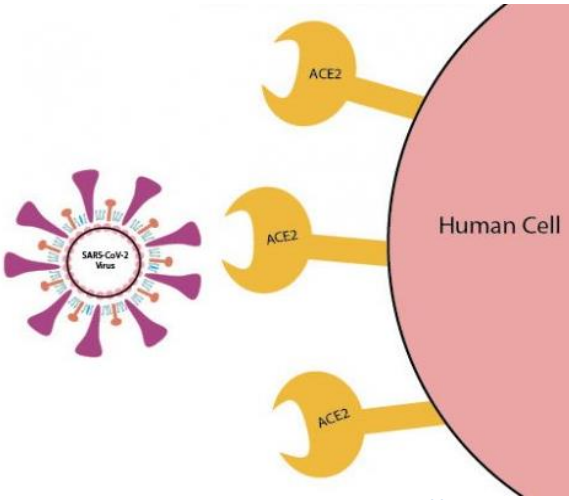

Figure 2. ACE2 Receptors[32]

The SARS-CoV-2 infection process begins with the attachment of Protein S to the ACE2 receptor, then SARS-CoV-2 enters the host cell and releases RNA.[8,32] In the host cell, the RNA genome is translated into polyprotein (pp1a/pp1ab), then replicated (split) into small products by viral proteinases. The polymerase enzyme produces a series of subgenomic mRNAs through RNA replication which ultimately translates into relevant viral proteins. The new viral proteins and genomic RNA are then assembled into virions in the endoplasmic reticulum, and the Golgi is then transported through vesicles,[8] eight released out of the cell and can infect other cells.[8,32] The process can be observed in figure 2.

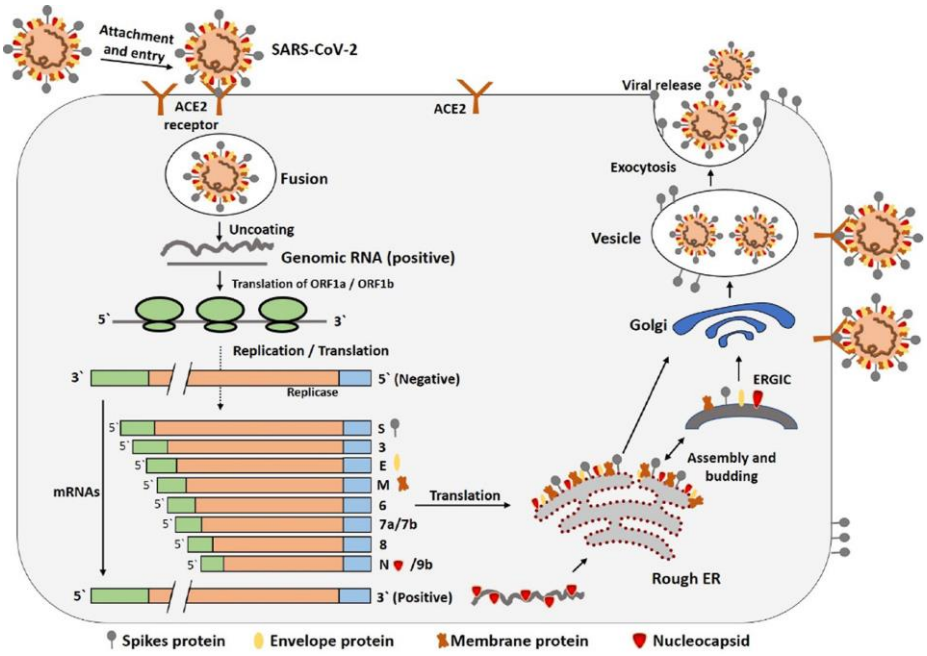

Figure 3. How SARS-CoV-2 Infects Humans[8]

Immune response to human

Humans have the body's defence against various microorganisms, especially those that are pathogenic. This defence system has a complex and complex defence mechanism.[33] The defence system is called the immune system.[34] A person's immune response to an antigen depends on the ability to do the right reaction to eliminate the antigen.[35] This ability is possessed by the components of the immune system that are found in the lymphoreticular tissue which is located throughout the body, for example in the lymph glands; respiratory tract; digestive tract; and other organs.[36]

One of the body's efforts to defend itself against the entry of antigens, such as viruses, is to destroy the virus non-specific (innate) with the process of phagocytosis, in this case, leukocytes and macrophages, including phagocytic cells that play an important role.[37,38] Besides being non-specific, the process of destroying antigens is also done specifically (adaptive). These specific defence mechanisms produce very small groups of proteins called antibodies.[39] These antibodies bind to specific antigens which then facilitate the destruction of antigens, the synthesis of these antibodies is encoded by DNA arranged together with the preparation of a new genome.[34,40]

In the human body, there is a defence system called the immune system. The body's immune system functions to help repair DNA; prevent infections caused by fungi, bacteria, viruses, and other organisms; and produce antibodies to combat antigen attacks.[34] Its job is to find and damage foreign organisms and their toxin products that can harm the human body.[37] When antigens enter the human body, the body will automatically give a response called the immune response. Immune responses that are generally formed consist of 2 types, namely innate immune responses and adaptive immune responses.[41]

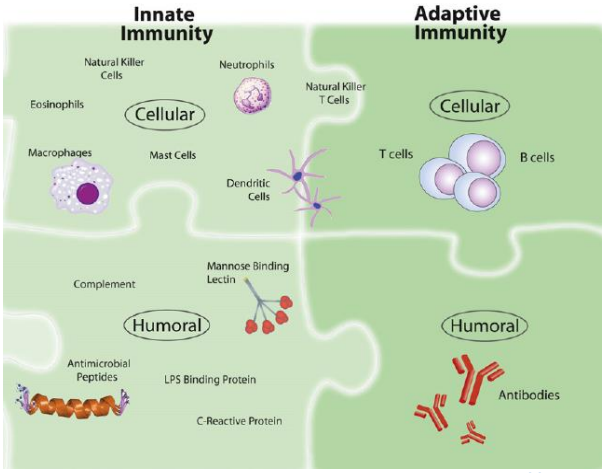

Figure 4. Innate and Adaptive Immunity[38]

The innate immune response becomes the first line of defence against antigens that enter the body, and then this response will trigger another immune response called the adaptive immune response.[42] This adaptive immune response then helps the innate immune work and is tasked with remembering the antigens that infect the body to prevent future infections.[39]

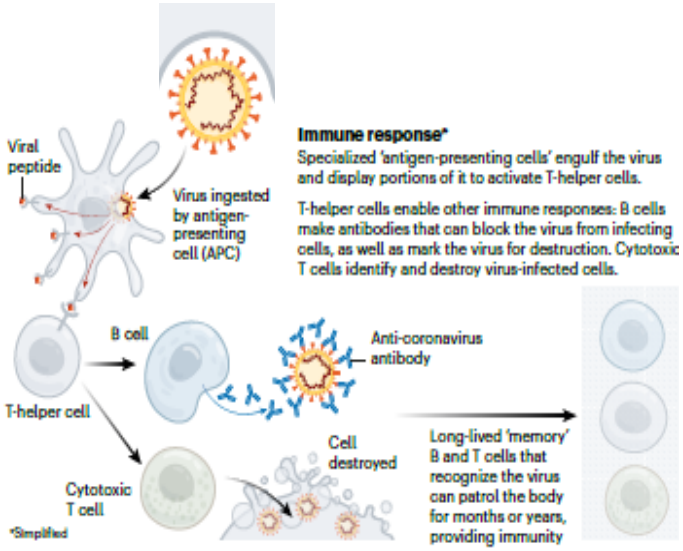

Figure 5. Immune Response to SARS-CoV-2[32]

The immune system can work when antigens are captured by antigen-presenting (APC) cells, and they will swallow viruses and display viral peptides on active T-helper cells. T-helper cells then send signals to other immune cells, such as cytotoxic T cells and B cells. Cytotoxic T cells will then identify and destroy cells infected with SARS-CoV-2, whereas B cells will recognize SARS-CoV-2 and form antibodies against SARS-CoV-2 antigens. Long-term memory of T cells and B cells can be in the body for a long time and can provide immunity when SARS-CoV-2 re-enters the host body.

Innate immune response

The innate immune response is the response carried out by the innate immune system that first appears when antigens begin to infect.[39] The innate immune response has cellular and humoral systems, including cellular immune systems mediated by natural killer cells (NK), eosinophils, monocytes, basophils, mast cells, and phagocytes (dendritic cells; macrophages; neutrophils.[38] NK cells are part of lymphocytes that can kill target cells directly without causing allergies.[40] Eosinophils are part of leukocytes which make up 1-6% of total leukocytes and many appear in allergies.[43] Monocytes are parts of leukocytes which account for 3-8% of total leukocytes and are classified as mononuclear phagocytes that have receptor sites on the membrane surface.[43] Basophils are the smallest part of leukocytes (less than 2%) and play a role in hypersensitivity reactions that are associated mainly with IgE.[43] Mast cells are cells that contain lots of granules that contain histamine and heparin.[42]

Phagocytes consisting of dendritic cells, macrophages, and neutrophils.[43] Dendritic cells are cells that process antigenic material and present it on the cell surface to be recognized by other immune cells, called antigen-presenting cells (APC), these cells serve as a connecting bridge between innate and adaptive immunity.[44] Macrophages are the main mononuclear phagocyte cells in the tissue in the process of phagocytosis against foreign molecular complexes, monocytes that leave the blood circulation can become macrophages.[45] Neutrophils, which are part of leukocytes that make up 50-70% of the total leukocytes and function as a defensive line that is phagocytic and can enter the infected tissue.[46]

In addition to the cellular immune system, there is also a humoral immune system that plays a role in the innate immune response, namely complement, mannose-binding lectin, antimicrobial peptides, LPS binding protein, and C-reactive protein.[39] Complement is a serum protein that is activated by an antigen that functions as an enzyme in helping protect the body from infection.[47] Mannose-binding lectin is a lectin that acts as a receptor connecting the virus with phagocytes.[42] Antimicrobial peptides are peptide components in the form of amino acids located on the surface of epithelial cells, which help increase immunity by functioning as an immunomodulator.[48] LPS binding protein is a serum lipid-binding glycoprotein that activates monocytes and macrophages to release inflammatory cytokines.[49] C-reactive protein is an inflammatory protein found in plasma and appears in acute phase infections.[50]

The innate immune response, plays an important role in response to SARS-CoV-2, the first response to an incoming virus is regulated mainly by alveolar macrophages, dendritic cells, airway epithelial cells, innate lymphocytes, and neutrophils.[51] Macrophages then present CoV antigens to T cells.[52] This process leads to activation and differentiation of T cells, including the production of cytokinins associated with T cell parts, followed by massive cytokinin release for the amplification of the immune response.[52,53] Cytokines are polypeptides that are produced in response to antigens that mediate and regulate immunological actions and inflammatory reactions.[53] The component of the innate immune response that arises due to SARS-CoV-2 infection in COVID-19 patients is presented in table 1.

Table 1. Default Immune Response to SARS-CoV-2 infection[12,53,54,55]

No	Type of innate immune	The amount
1	Cytokines (IL-1β, IL-2, IL-6, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α / CCL3 and TNF)	increased
2	Coagulation parameter (D-dimer)	increased
3	Neutrophil	increased
4	C-reactive protein	increased
5	Total lymphocytes	decreased

Table 1 shows that in COVID-19 patients the total lymphocytes (T lymphocytes and B lymphocytes) in the blood are significantly decreased, inflammatory cytokinins such as IL-6 will also increase significantly, coagulation parameters such as D-Dimer increase abnormally, so CT shows expansion of lung lesions, other immune systems that are also affected by SARS-CoV-2 namely neutrophils and significantly increased C-reactive protein.[53] Adults infected with SARS-CoV-2 can experience a decrease in lymphocyte counts until lymphocytopenia occurs, especially those who suffer from severe illness. In children with SARS-CoV-2, peripheral blood lymphocytes remain largely in the normal range and show more immune dysfunction.[53]

In a report on 99 cases in Wuhan, the immune response formed by SARS-CoV-2 infection increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum IL-6 (52%) and increased protein c -reactive (84%).[12] Most of the severe COVID-19 patients experienced markedly elevated serum pro-inflammatory cytokinin levels including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1 , MIP1α (CCL3) and TNF, which are characterized by cytokine storm syndrome. C-reactive protein and D-dimer are also found to be very high.[54] Research in Wuhan, China, shows that COVID-19 damages T lymphocyte cells by reducing the number of T lymphocytes to lymphocytopenia in 44% of 452 patients with congenital diseases (hypertension, diabetes, chronic obstructive pulmonary disease). In this severe group, there was also an increase in the number of pro-inflammatory neutrophils and cytokines (TNF-α, IL-1, IL-6, and IL-8).[55] High levels of pro-inflammatory cytokines can cause shock and damage to some tissues, such as the heart; heart; and kidney, and respiratory failure due to mediating extensive pulmonary pathology, which leads to infiltration of neutrophils and macrophages, diffuse alveolar damage with hyaline membrane formation, and diffuse thickening of the alveolar wall.[56] In addition, splenic atrophy and lymph node necrosis in patients who die also results from excessive immunity.[56,57]

Adaptive immune response

The adaptive immune system is a development of the innate immune system. The adaptive immune system has the advantage of immunological memory, but it is entirely dependent on the innate immune system as the originator of the response. Interactions of the innate and adaptive immune systems that lead to the efficient introduction of antigens, but mal-adaptive interactions between the two can cause dangerous immunology such as allergies and autoimmune.[43]

The adaptive immune response also has a cellular and humoral system. Cellular systems in adaptive immune responses include T cells[38] namely cellular immunity that plays a role in the specific immune system consisting of CD4 + cells, CD8 + cells, naive T cells, NK T cells, and Th3,[58] B cells[38] a collection of cell populations that express various immunoglobulin receptors on the cell surface to recognize various antigens,[59] and dendritic cells that act as a link between the innate immune system and the adaptive immune system.[38]

As for the humoral system in the adaptive immune response that is mediated by antibodies (immunoglobulins secreted by B cells).[38] Immunoglobulin (Ig) is a molecule found in plasma that can specifically respond to antigens that stimulate its production. Immunoglobulin is a heterotetramer molecule that contains four polypeptide chains consisting of two long chains called heavy chains (H), and two short chains called light chains (L).[60] Data on adaptive immune responses that arise due to SARS-CoV-2 infection are presented in table 2.

Table 2. Adaptive Immune Responses to SARS-CoV-2 Infection[56,60]

No	Adaptive immune type	The amount
1	Total antibody titer	increased
2	Immunoglobulin M	increased
3	Immunoglobulin G	increased

In COVID-19 patients, it was reported that patients with severe disease often experienced increased IgG responses and higher total antibody titers, which were associated with poorer outcomes from SARS-CoV-2 infection.[57] Research conducted in China in March 2020, showed that of 173 patients known to have a total antibody titer increased 93.1% on the 11th day, IgM increased 82.7% on the 12th day, and IgG increased 64.7% on the day 14th, with 12 patients were found to have negative antibodies which may be a lack of blood samples at a later stage of the disease.[56] Antibodies can neutralize viruses by inhibiting the attachment of viruses to receptors on host cells, thereby preventing intracellular penetration and multiplication.[61] IgM and IgG antibodies in the human body are present in the serum. Serum COVID-19 patients who have recovered can be used for therapy of COVID-19 patients who have not healed because they contain antibodies.[60,61] Convalescent plasma therapy in COVID-19 patients out of 5 patients showed viral elimination and increased antibody titer in 2 patients, also showed improvement in lung lesions in patients on the third day after plasma transfusion.[60]

Viruses may remain uncontrolled despite an increase in host immunity because the virus has mutated during the transmission process in the host body.[7] RNA virus mutations contribute to the adaptation of viruses in creating a balance between the integrity of genetic information and genomic variability.[20,62] The sequence of mutations is identified singly or double in coding 3C-Like Protease from a virus that is resistant to inhibitors. Inhibited resistant viruses show delays and reduce the production of infectious virus particles.[63] The ability of the virus to defeat the immune response makes the immune response inadequate, causing viral replication and tissue damage. On the other hand, an excessive immune response can also cause autoimmune diseases.[15] Autoimmune occurs when the immune system that is formed incorrectly identifies antigens, where cells, tissues or organs of the human body are actually considered as foreign objects so that they are damaged by antibodies.[64]

4. CONCLUSION

SARS-CoV-2 is known only to be able to infect if it finds an appropriate receptor, in this case, the ACE2 receptor. Viruses that have entered cells can divide RNA and damage cells, new viruses that form will exit the cell and infect other living cells. COVID-19 has an asymptomatic incubation period of 2-14 days, during which time the body will form an immune response. These immune responses include increasing levels of cytokines, coagulation parameters, C-reactive protein, neutrophils, and decreasing total lymphocytes. It is also known that COVID-19 patients with severe disease often experience higher total antibodies, IgM responses, and IgG responses than COVID-19 patients without congenital diseases. This review was carried out while the COVID-19 pandemic was still ongoing, so that not many published research data were available, it is hoped that further studies and reviews related to the human immune response to SARS-CoV-2 infection with more data would be obtained to obtain deeper and larger knowledge.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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