



# **The Dynamics of Innate and Adaptive Immune Response to Sars Cov-2 Infection and Its Limitations in Human Beings**

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*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

This article deals with the dynamics of the innate and adaptive immune response to severe acute respiratory syndrome coronavirus 2 (SARSCoV2) infection. SARSCoV2 is the viral factor that causes the current global coronavirus pandemic disease 2019 (COVID2019).

In terms of person-to-person transmission, it is contacted by inhaling the sneeze droplets of infected people. Severe acute respiratory syndrome Coronavirus 2 attacks lung cells first in its binding mechanism because there are many conservative receptor entries, such as angiotensin converting enzyme 2. The presence of this virus in host cells triggers a variety of protective immune

responses, resulting in leads to pneumonia and acute respiratory distress syndrome. In the SarsCoV2 infection process, virus replication, immune response, and inflammatory response are dynamic events that can change rapidly; leading to different results, involving the dynamic expression of pro-inflammatory genes, peaking after the lowest point of respiratory function and leading to a cytokine storm, research on the interleukin 1 (IL1) pathway has shown that it is a factor related in severe respiratory diseases. The weakened expression of cytokines associated with mild infections will also delay T cell immunity to SARSCoV2, thereby prolonging the infection time; this indicates that such afebrile (afebrile) infections and undifferentiated COVID19 cases may promote the virus in the community Spread. This review aims to provide a general overview of the dynamics involved in the human immune response to this viral infection. It also includes a brief description of its structure, discovery history and pathogenesis to facilitate the understanding of this article.

*Keywords: Dynamics; innate and adaptive immune response; SARS CoV-2 infection; limitations in human beings.*

## 1. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2) is a virus that is the cause of a new viral acute respiratory disease in humans. Its discovery date is commonly named Coronavirus Disease 2019 (COVID2019). The mutation between SARS CoV2 and COVID19 means that the Coronavirus 2 Syndrome (SARSCoV2) is the name of the new coronavirus in 2019. SARS CoV2 is a new type of coronavirus that has not been found in humans before, and COVID19 is the name of the disease related to this virus was discovered by the World Health Organization (WHO) on March 11, 2020 as a new coronavirus pandemic [1] SARS CoV2 is an enveloped, unsegmented, single-stranded, positive-stranded RNA virus [2]. Historical records show that Almeida and David Tyrrell. In 1933, virus was renamed infectious bronchitis virus (IBV) [3]. The human strain of coronavirus was first discovered in the respiratory tract of patients at the Chinese seafood market in Hubei and Wuhan in December 2019 was identified as a newly discovered new type of beta coronavirus (nCoV) Guo et al in December 31, 2019. The teams of Wu and Zhou in Wuhan, China named it WHHuman1 and 2019nCoV1 (Wu et al., 2020) simultaneously produced studies conducted through genome sequencing showed that bats are suspected to be the hosts of the virus. The host, because their genome is 96.2% identical to CoV RaTG13 bat [4]. During human infection, angiotensin converting enzyme 2 (ACE2) acts as a receptor on the host cell membrane. On February 27, 2020, the World Health Organization officially named the COVID19 infection and virus SARSCoV2 [5].

Its rapid transmission and acute infection, high rate of mortalities and morbidities has made it a global threat to human existence [4]. As of 14th March 2021, at least 2013 deaths, 160,537 confirmed cases and 205 new cases in Nigeria have been reported by WHO global health observatory statistics (WHO.2021).

Rapid spread of SARS-CoV-2 within our population is facilitated by the structural virulence nature and severe oppressive mechanism of this virus. Lung cells are the first point of attack through many entry receptors such as Angiotensin Converting Enzyme2.

The presence of this virus in host cells triggers various protective immune responses leading to pneumonia and Acute Respiratory Syndrome. Innate and adaptive response are the defensive machineries involved in the immune response dynamics process. SARS-CoV-2 infections, especially in the early phase of illness, are indeed dynamic.

Dynamic expression of pro-inflammatory genes, which most of these genes peaked after the nadir of respiratory function brings in cytokine storm, According to research data of [6] which reveals the possibility that the interleukin-1 (IL-1) pathway may be one of the suitable correlate contributing to severe respiratory disease in Sars-Cov-2 infection. In addition, the attenuated cytokine expression associated with mild infection could also delay T cell immunity against SARS-CoV-2, which prolongs infection; this suggests the possibility that its infection without fever (afebrile) and undifferentiated COVID-19 cases may drive virus spread in the community [6].

The changes observed particularly affect the elderly persons with immune-senescence and persons with previous ailment immune derangement. Example an index case 1, 2,3 study of a 66, 37, and 38 years old man and his sons by Kim et al. These findings revealed the dynamics shown as first, Case 1 66years had reduced activation of adaptive immune genes, which unleashed the toll-like receptor TLR-mediated pro-inflammatory response which affirms an experimental study that found that reduced T cell activation potentiates TLR-mediated inflammation in a positive feedback loop. Second and alternatively, increased expression of pro-inflammatory mediators in Case 1 could have led to recruitment of CD4+ and CD8+ T cells from the peripheral blood to sites of infection and the draining lymph nodes. That could have led to the mostly negative RT-PCR finding in the throat swabs from Case 1. In contrast, Case 2 of 37 years and Case 3 of 38 years old sons had lower pro-inflammatory responses with elicited mild symptoms and more attenuated T cell activation. Case 2 was afebrile throughout the period of isolation, and his cough resolved 10 days before SARS-CoV-2 RT-PCR became negative. However, with an attenuated T cell response, SARS CoV-2 became prolonged as shown by the consistent viral RT-PCR positivity that lasted for nearly a month. In either case, our data suggests an important role for T cells in COVID-19. Defining the role of T cells in either the pathogenesis of severe COVID-19 or prolonged SARS CoV-2 infection should thus be a priority, as the understanding of this would impact case management and virus transmission control, respectively [6].

In view of this it is advisable that persons of this category should adopt extra strategies to boost their immune status in addition to observing non pharmaceutical interventions (NPI) precautions to stay safe, healthy and alive.

This paper was written to review the dynamics involved in the mechanism of innate and adaptive immune response to sars-cov-2 infection in human and the limitations of innate and adaptive immune response at the course of immune response to Sars-cov-2infection in human beings.

## 2. DISCOVERY HISTORY OF SARS-COV-2

The first report of coronavirus infection discovery was from animals in the late 1920s, when a new

type of upper-respiratory tract disease occurred among chickens in North Dakota, United State of America in 1931.

The causative agent was identified as a virus in 1933. By 1936, the disease and the virus were recognized as viral disease known as infectious bronchitis virus (IBV), but later officially renamed as avian coronavirus. A new brain disease of mice (murine encephalomyelitis) was discovered in 1947 at Harvard Medical School in Boston. The virus causing the disease was called JHM after Harvard pathologist John Howard Mueller. Three years later anew mouse hepatitis was reported from the National Institute for Medical Research in London. The causative virus was identified as mouse hepatitis virus (MHV) [7].

In 1961 a virus was obtained from a school boy in Epsom, England, who was suffering from common cold. The sample designated B814 was confirmed as novel virus in 1965. New common cold viruses (assigned 229E) collected from medical students at the University of Chicago were also reported in 1966. Structural analyses of IBV, MHV, B18 and 229E using transmission electron microscopy revealed that they all belong to the same group of viruses. Making a crucial comparison in 1967, June Almeida and David Tyrrell invented the collective name coronavirus, as all those viruses were characterized by solar corona-like projections (called spikes) on their surfaces [8].

Coronaviruses have been discovered from pigs, dogs, cats, rodents, cows, horses, camels, Beluga whales, birds and bats. As of 2020, 39 species are described. Bats are found to be the richest source of different species of coronaviruses. All coronaviruses originated from a common ancestor about 293 million years ago. Zoonotic species such as Severe acute respiratory syndrome-related coronavirus (SARS-CoV), Middle East respiratory syndrome-related coronavirus (MERS-CoV) and Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), are the aetiological agent of the COVID-19 pandemic.

Evolutionary history reveals chicken coronavirus, mouse coronaviruses, and human coronaviruses. However according to phylogenetic study all coronaviruses evolved from the most recent common ancestor that lived around 190 to 489 (with a mean of 293) million years ago. The four genera split up to 2,400 to 3,300 years ago into

bat and avian coronavirus ancestors. Bat coronavirus gave rise to species of *Alphacoronavirus* and *Betacoronavirus* that infect mammals, while avian coronavirus produced those of *Gammacoronavirus* and *Deltacoronavirus* that infect birds. Zoonotic coronaviruses emerged recently. For instance, SARS-CoV was transmitted from bats in 1998 (4.08 years prior to the outbreak), and diverged from bat coronavirus in around 1962. SARS-CoV-2 evolved from bat coronavirus in around 1948.

Coronaviruses that are transmitted from animals (zoonosis) are clinically the most important human coronaviruses as they are responsible for a series of global epidemics. Two species of zoonotic human coronaviruses are the Severe acute respiratory syndrome-related coronavirus (SARS-CoV), Middle East respiratory syndrome-related coronavirus (MERS-CoV) and now the newly discovered Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2).

## 2.1 Discovery of Human Coronaviruses

Human coronaviruses were discovered as one of the many causative viruses of common cold. Research on the study of common cold originated when the British Medical Research Council and the Ministry of Health established the Common Cold Research Unit (CCRU) at Salisbury in 1946 [9]. Andrewes, directive work in the research laboratory discovered several viruses such as influenza viruses, *Parainfluenza* viruses and rhinoviruses that cause common cold [10].

David Arthur John Tyrrell joined CCRU in 1957 and succeeded Andrewes in 1962. "David and Tyrrell CBE: 1925 –2005). He developed a technique for growing rhinoviruses using nasal epithelial cells for the first time in 1960 (Tyrrell and Parsons [11]. His team soon after developed a concept of broad categorization of common cold viruses into two groups: one group, called H strain, because it could only be maintained in human-embryo-kidney cell culture, and another group, designated M strain, could be maintained both in human-embryo-kidney cell culture and monkey-embryo-kidney cell culture. By then many common cold viruses could be grown in either of these cell cultures and were accordingly classified as M or H strain [12].

During 1960-1961, Tyrrell's team collected throat swabs from 170 school boys having common cold at a boarding school in Epsom, Surrey, England. Among few samples that could not be cultured in any of the culture media, a specimen designated B814, collected on 17 February 1961, was particularly infectious among healthy volunteers [12]. There was no evidence whether the pathogen in B814 was a bacterium or a virus as all bacterial and viral culture methods available showed negative results. It could only be maintained in human tracheal culture and experimentally passed on to healthy volunteers by nasal inoculation [13]. In 1965, they were able to confirm that the pathogen was a filter-passing virus, susceptible to ether treatment (indicating a lipid envelope of the virus), able to induce cold in antibiotic-treated volunteers (indicating it was not a bacterium), and cultured in human-embryo-trachea epithelial cell culture. Serological tests (antigen-antibody reactions) further indicated that the virus was not related (not reactive) to antibodies (serotypes) of any known viruses at the time [7]. Reporting in the British Medical Journal, Tyrrell and Malcolm L. Bynoe wrote their conclusion as After considerable initial doubts we now believe that the B814 strain is a virus virtually unrelated to any other known virus of the human respiratory tract, although, since it is ether-labile, it may be a myxovirus [14].

But they contradicted themselves regarding the identity of the virus as they mentioned in the experimental results, saying: It was concluded that B814 did not belong to any of the serotypes of myxovirus used, but might be distantly related to influenza C or Sendai viruses [14]. In an independent research in United States of America, Dorothy Hamre and John J. Procknow studied respiratory tract infection among medical students at the University of Chicago [15]. In 1962, they obtained five samples that were associated with very different symptoms, causing mild cold only, and could be cultured only in secondary human kidney tissue in contrast to other cold viruses which could be maintained in monkey-embryo-kidney cell culture. Serological test indicated they were not *myxoviruses* (*Orthomyxoviridae*). They presented their discovery as "A new virus isolated from the human respiratory tract" in the Proceedings of the Society for Experimental Biology and Medicine in 1966 [16]. They further studied one sample, designated 229E, grown in human diploid cell culture (Wi-38) and described its developmental stages using transmission

electron microscopy to show that it was new type of virus.

## 2.2 Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV)

Two distinct viruses are known under this species, namely SARS-CoV and SARS-CoV-2. SARS-CoV emerged as an acute respiratory syndrome in Guangdong Province, southern China, during 16 November 2002 to 28 February 2003 [17]. The syndrome was accompanied by pneumonia that was fatal in many cases [18]. The infection was believed to have been contained in China, but an infected individual carried it to Hong Kong on 21 February and spread it in the hospital [19]. The first clinical case outside China was reported on 26 February 2003 in Hanoi, Viet Nam. It rapidly spread to Southeast Asia, North America and Europe. The World Health Organization (WHO) notified an epidemic alert on 6 March 2003, referring to the disease as severe acute respiratory syndrome [20]. The virus was identified as a novel coronavirus from Hong Kong in April, from Toronto in May, and at the Centers for Disease Control and Prevention (CDC) in U.S in May [21]. In October, the samples from Guangdong were established as the prototype specimens, and the name SARS coronavirus (SARS CoV) was introduced (ICTV.2003) [22]. By mid-July 2003, the infection subsided, and by then it had spread to 28 countries infecting 8096 people and causing 774 deaths [19]. In October, it was found that the infection was acquired from the masked palm civets (*Paguma larvata*) from a live-animal market in Guangdong Guan et al. [23]. Further studies in 2005 showed that civets were the intermediate reservoirs of the virus, and horseshoe bats (*Rhinolophus species*) were the natural hosts [24].

Infection with SARS-CoV-2 was known from cases of atypical pneumonia in Wuhan, China [25]. The Wuhan Municipal Health Commission reported 27 individuals having "viral pneumonia" on 31 December 2019. The first known case was recorded on 12 December [26]. The first case outside China was in Thailand on 13 January. WHO adopted the name of the disease as "coronavirus disease 2019" (COVID-19) on 11 February 2020, and used "2019 novel coronavirus" or "2019-nCoV" for the virus. www.who.int.2020 On 2 March 2020, ICTV published the formal description and gave the official name as Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). WHO declared the infection as pandemic on 11

March, and since then has spread around the world, affecting over 178 million people and resulting in more than 3.86 million deaths [26]. The origin of the virus is not known. Malayan pangolins (*Manis javanica*) which are available in the live-animal market in Wuhan city has been studied as a probable source as the virus is closely related to the pangolin coronavirus [27]. Genetic evidence that it bears 93% nucleotide similarity with a novel coronavirus of Malayan horseshoe bat (*Rhinolophus malayanus*) [28] and 96% identity with Bat SARS-like coronavirus RaTG13 of intermediate horseshoe bat (*R. affinis*) indicates that it probably originated in bats [28].

## 3. CLASSIFICATION OF SARS-COV-2

SARS-COV-2 is a species of coronavirus that infect human).Molecular Evolution of Human Coronaviruses Genomes has been traced to have their origin in bats. The human coronavirus NL63 shared a common ancestor with a bat coronavirus (ARCoV.2) between 1190 and 1449 CE.The human coronavirus 229E shared a common ancestor with a bat coronavirus (GhanaGrp1Bt CoV) between 1686 and 1800 CE. More recently, alpaca coronavirus and human coronavirus 229E diverged sometime before 1960. MERS-CoV emerged in humans from bats through the intermediate host of camels. MERS-CoV, although related to several bat coronavirus species, appears to have diverged from these several centuries ago.The most closely related bat coronavirus and SARS-CoV diverged in 1986 [29]. The ancestors of SARS-CoV first infected leaf-nose bats of the genus *Hipposideridae*; subsequently, they spread to horseshoe bats in the species *Rhinolophidae*, then to Asian palm civets, and finally to humans. This constitutes the scientific basis of the taxonomic classification of coronaviruses where human coronaviruses is inclusive.

Coronaviruses constitute the subfamily *Orthocoronavirinae*, in the family *Coronaviridae*, order *Nidovirales*, and realm *Riboviria* [30]. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry.The genome size of coronaviruses ranges from approximately 26 to 32 kilobases, one of the largest among RNA viruses [31]. They have characteristic club-shaped spikes that project from their surface, which in electron micrographs create an image reminiscent of the solar corona, from which their name derives

### 3.1 Evolutionary Classification Trend of Coronaviruses

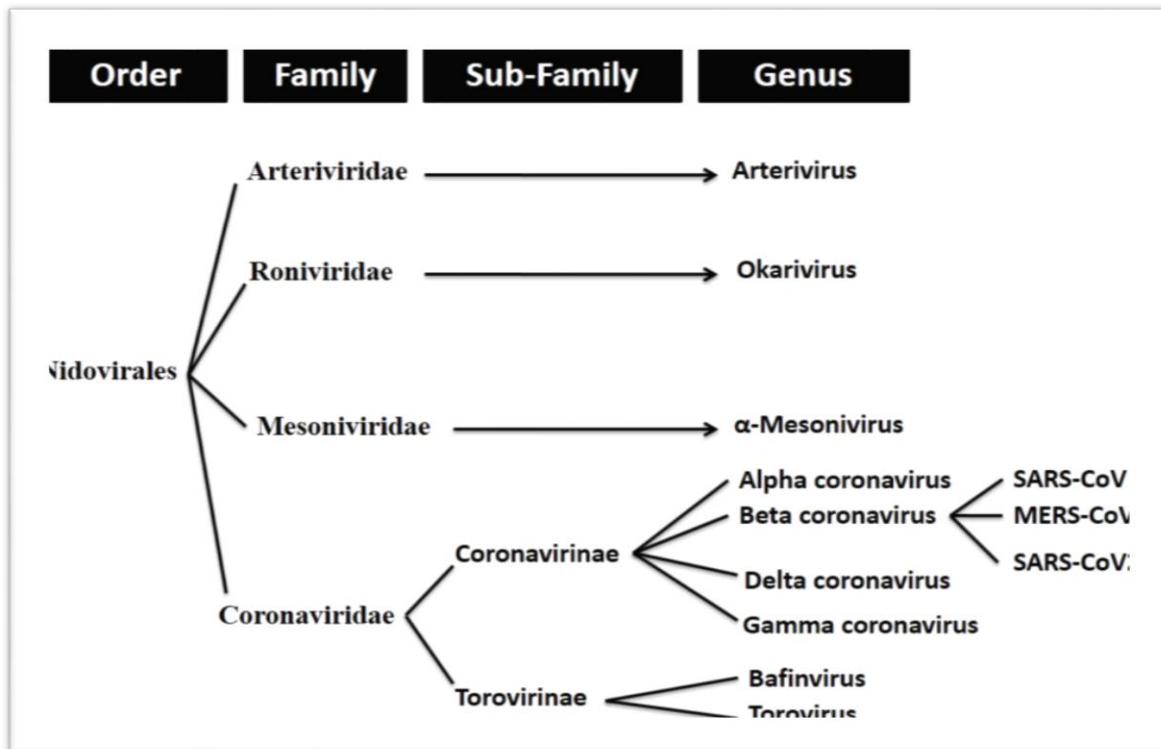


Fig. 1. Classification of coronaviruses. Adapted from “Evolutionary Trajectory for the Emergence of Novel Coronavirus SARS-CoV-2”, by Saif ur Rehman et al. [32] retrieved from <https://www.mdpi.com/2076-0817/9/3/240/htm>.

### 4. STRUCTURE OF SARS -COV-2

Coronaviruses are large, roughly spherical particles with unique surface projections. Their size is highly variable with average diameters of 80 to 120 nm. Extreme sizes are known from 50 to 200 nm in diameter. The total molecular mass is on average 40,000 kDa. They are enclosed in an envelope embedded with a number of protein molecules. The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell [33].

A sample isolation from pneumonia patients who were some of the workers in the Wuhan seafood market found that strains of SARS-CoV-2 had a length of 29.9 kb. Structurally, SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins [34]. The spike or S glycoprotein is a trans membrane protein with a molecular weight of about 150 kDa found in the outer portion of the virus. S protein forms homotrimers protruding in

the viral surface and facilitates binding of envelope viruses to host cells by attraction with angiotensin-converting enzyme 2 (ACE2) expressed in lower respiratory tract cells. This glycoprotein is cleaved by the host cell furin-like protease into 2 sub units namely S1 and S2. Part S1 is responsible for the determination of the host virus range and cellular tropism with the receptor binding domain make-up while S2 functions to mediate virus fusion in transmitting host cells [35].

The nucleocapsid known as N protein is the structural component of CoV localizing in the endoplasmic reticulum-Golgi region that structurally is bound to the nucleic acid material of the virus. Because the protein is bound to RNA, the protein is involved in processes related to the viral genome, the viral replication cycle, and the cellular response of host cells to viral infections. N protein is also heavily phosphorylated and suggested to lead to structural changes enhancing the affinity for viral RNA [36].

Another important part of this virus is the membrane or M protein, which is the most structurally structured protein and plays a role in determining the shape of the virus envelope. This protein can bind to all other structural proteins. Binding with M protein helps to stabilize nucleocapsids or N proteins and promotes

completion of viral assembly by stabilizing N protein-RNA complex, inside the internal virion. The last component is the envelope or E protein which is the smallest protein in the SARS-CoV structure that plays a role in the production and maturation of this virus [35].

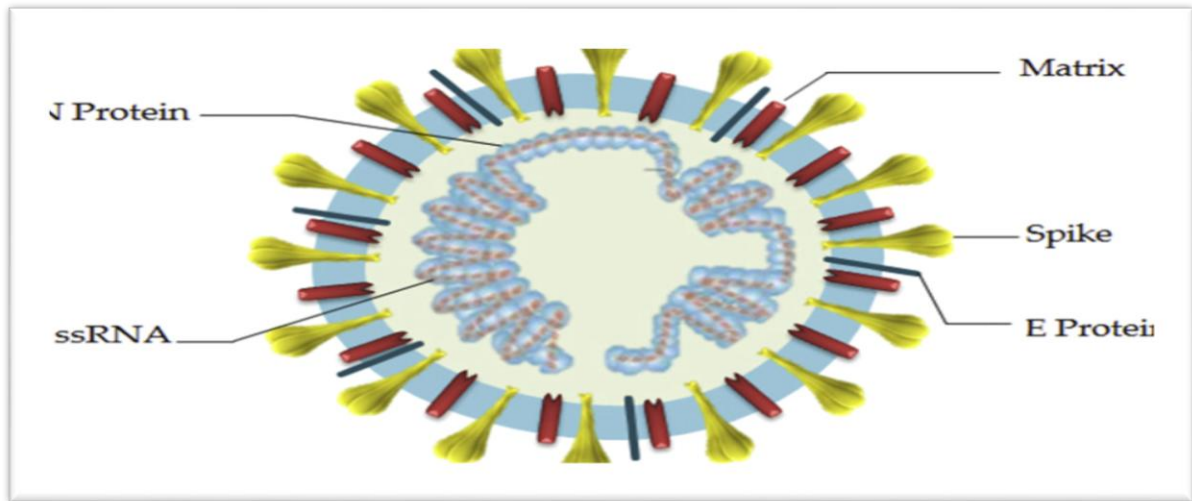


Fig. 2. Structure of severe acute respiratory syndrome coronavirus.2 (SARS-CoV-2) (Schoeman and Fielding, 2019).

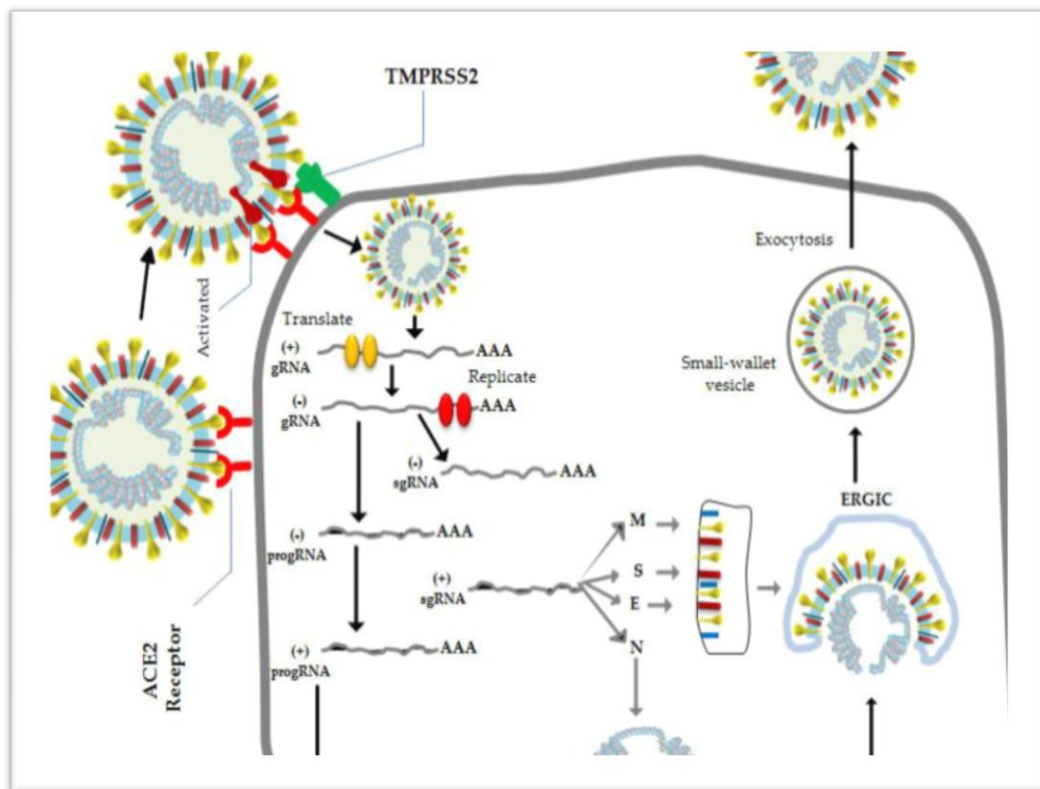


Fig. 3. Illustrative Diagram of the Pathogenesis of SARA-CoV-2 in Human [38]

In supporting the process of entry of the virus into the host cell, SARS-CoV-2 binds to the ACE2 receptor that is highly expressed in the lower respiratory tract such as type II alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells, and other cells such as absorptive enterocytes from the ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells. Therefore, patients who are infected with this virus not only experience respiratory problems such as pneumonia leading to Acute Respiratory Distress Syndrome (ARDS), but also experience disorders of heart, kidneys, and digestive tract [37].

## **5. PATHOGENESIS OF SARS COV-2 INFECTION IN HUMAN**

Illustration from Fig. 3 shows that pathogenesis of coronavirus (Sars-Cov-2) begins when the human comes in contact with the virus through its entry point, the virus infection and disease is established through a life cycle of replication as explained as follows:

### **5.1 Entry and Life Cycle of Coronaviruses**

A member of the Nidovirus family, coronavirus infection (SARS-CoV2) can be contracted from animals such as bats, and fellow humans. This virus can enter the human body through its receptors, ACE2 which are found in various organs such as heart, lungs, kidneys, and gastrointestinal tract, thus facilitating viral entry into target cells. The process of CoV entering into the host cell begins with the attachment of the S glycoprotein to the receptor, the ACE2 in the host cells (such as in type II pneumocytes in the lungs). This attachment occurs in the binding domain of S protein of SARS-CoV-2 receptors which are present at 331 to 524 residues, and can bind strongly to human ACE2 and bat ACE2. The entry and binding processes are then followed by fusion of the viral membrane and host cell.

After fusion occurs, the type II trans-membrane serine protease (TMPRSS2) that is present on the surface of the host cell will clear the ACE2 and activate the receptor-attached spike-like, S proteins [38]. Activation of the S proteins leads to conformational changes and allows the virus to enter the cells [39]. Both of these proteins (TMPRSS2 and ACE2) are the main determinants of the entry of this virus. Based on the research of Sungnak et al. nasal epithelial cells, specifically goblet/secretory cells and

ciliated cells, display the highest ACE2 expression throughout the respiratory tract. The entered-SARS-CoV-2 releases its genomic material in the cytoplasm and become translated in the nuclei [33].

The genomic material released by this virus is mRNA that is ready to be translated into protein. In its genome range, this virus is complemented by about 14 open reading frames (ORF), each of which encodes a variety of proteins, both structural and non-structural that play a role in its survival as well as virulence power. In its phase of transformation, the gene segments that encode nonstructural polyproteins are the ones this process first translates into ORF1a and ORF1b to produce two large overlapping polyproteins, pp1a and pp1ab by contributing a ribosomal frame shifting event (Masters 2006). The polyproteins are supplemented by protease enzymes namely papain-like proteases (PLpro) and a serine type Mpro (chymotrypsin-like protease (3CLpro)) protease that are encoded in nsp3 and nsp 5. Subsequently, cleavage occurs between pp1a and pp1ab into nonstructural proteins (nsps) 1–11 and 1–16, respectively. The nsps play an important role in many processes in viruses and host cells infection.

## **6. INNATE AND ADAPTIVE IMMUNE RESPONSE TO SARS-COV-2 IN HUMAN BEINGS**

The body's immune response to SARS-CoV-2 and SARS-CoV is closely similar and are mediated by cytokines [40]. A case report in Wuhan from 99 COVID-19 patients revealed that there was an increase in the total number of neutrophils, Interleukin-6 (IL-6) serum and c-reactive protein about 38%, 52% and 86%, respectively and 35% decrease of total lymphocytes [41]. Other research found increased expression of proinflammatory cytokines and chemokines IP-10, MCP-1, MIP-1A, and tumor necrosis factor-alpha (TNF $\alpha$ ) [2]. These conditions are the cause of severity and mortality of this disease which suggest the potential of cytokines storm as found occurring in SARS-CoV and MERS-CoV infections [42].

### **6.1 Innate Immune Response to SARS-CoV-2**

The entry of the virus into the host cell triggers stimulation of the host's immune response, which will first be encountered by innate immune system cells through antigen presenting cells



(APC), example dendritic cells and macrophages as frontline team of the innate immune system [43]. APC have Pattern Recognition Receptors (PRR) including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and other small free molecules that are located in various places in host cells such as plasma membranes, endosomal membrane, lysosomes, endocytolysosomes, and cytosol. They recognize that PAMP involved in this process are nucleic acids, carbohydrate moieties, glycoproteins, lipoproteins and other small molecules that are found in the structural components of viruses or intermediate products such as dsRNA and induce cascade signaling to produce immune system cell effectors. Each of the PRRs could induce a different biological response to subsequent protein activation [44]. For example, Toll like receptor 4 (TLR-4) might recognize the outer component of CoV, example the protein spike. Furthermore, through mediation of MyD88, this introduction will trigger the activation of NF- $\kappa$ B transcription factors and the pathogen-activated protein kinases (MAPKs) pathway to induce proinflammatory proteins. Meanwhile, activation of endosomal receptors such as TLR-3 and TLR that could recognize the RNA or dsRNA genome of coronavirus leads to recruitment of TRIF adapter protein directly. TRIF subsequently activates the IRF3 and NF- $\kappa$ B transcription factors to induce proinflammatory cytokines such as interferon- $\alpha$  and TNF- $\beta$ . Although the introduction of PAMP through TLR-4 can also recruit TRIF adapter proteins, the recruitment must be mediated by TRAM and TIRAM [44]. This production of proinflammatory cytokines is the initial response in the first line of defense against virus infection. Furthermore, type I INF in turn will form complexes with its receptors, IFNAR and subsequently activate the JAK-STAT pathways. JAK1 and TYK2 kinases further phosphorylate STAT1 and 2 followed by its complexation with IRF9, and together they migrate into the nucleus to initiate the transcription of IFN-stimulated genes (ISGs) and lead to suppression of viral replication and prevent the severity of the disease [42]. However, excess releasing of pro-inflammatory cytokines such as IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF $\beta$ , and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 from immune effector cells causes hyperinflammation which will eventually lead to acute respiratory distress syndrome (ARDS) [45]. As the presenter of foreign antigens, the APC will present the antigen of CoV to the CD4 + T-helper cells by MHC class 1, and this leads to releasing

of IL-12 as a co-stimulatory molecule to further stimulate the Th1 cell activation. In addition to Th1 stimulation, releasing of interleukin-12 and IFN- $\alpha$ , an increase in MHC Class I expression and NK cell activation is also needed for resistance of viral replication for the eradication of virus-infected cells. It also initiates production of proinflammatory cytokines via the NF- $\kappa$ B signaling pathway. IL-17 is a proinflammatory cytokine that also is increased when SARS-CoV2 infection occurs. These cytokines further recruit neutrophils and monocytes to the site of infection and activate several other pro-inflammatory cytokines and chemokines including IL-1, IL-6, IL-8, IL-21, TNF- $\beta$ , and MCP-1 [43]. Next, activation of Th1 cells could stimulate CD8 + T cells, which are one of the effectors of T cells that will target and kill cells infected with CoV.

## 6.2 Adaptive Immune Response to SARS-CoV-2

CD4 T cells could stimulate humoral immune responses by producing antigen-specific antibodies through activating T-dependent B cells [44]. The antibodies produced are generally IgM and IgG which have a unique presence pattern in response to the presence of coronavirus [43]. Generally, this infection will produce a specific IgM that can only last 12 weeks, but IgG with a longer period. In addition to the formation of antibodies, exposure to this virus also cause the formation of CD4 T cells and CD8 memory that can last for four years Fan et al. [46]. Based on findings in patients who recovered six year after coronavirus infection, T cell memory was still able to hit the peptide spike when the first exposure occurred (Tang et al., 2011). This further explains and directs researchers to the development of vaccines against the corona virus, especially to SARS-CoV-2, which is now a pandemic outbreak worldwide [44].

## 7. DYNAMICS OF THE INNATE AND ADAPTIVE IMMUNE RESPONSES TO SARS-COV- 2 INFECTION IN HUMAN BEINGS

During the course of COVID-19 infection, viral replication, immune response, and inflammatory reaction are dynamic events that can change rapidly, resulting in different outcomes; several reports have presented these changes. Thevarajan et al. [47] reported the case of a patient with mild to moderate infection that was clinically, virologically, and immunologically

followed over the course of the disease, including her recovery 13 days after the initiation of symptoms, and through to Day 20 at which point she had recovered. The virus was detected on Days 4 and 5 via nasopharyngeal swabs but was undetectable thereafter. IgM and IgG anti-SARS-CoV-2 antibodies progressively increase from Day 7 through to Day 20. Circulating antibody-secreting B cells, CD3-CD19+CD27hiCD38hi, appeared in the blood at the time of viral clearance (Day 7), peaked on Day 8, and remained high through to Day 20. Follicular helper T cells (TFH), CD4+CXCR5+ICOS+PD-1+, were also detected on Day 7 and continued increasing through to Day 20. Activated cytotoxic CD8 T cells, CD8+CD38+HLA-DR+, were also present on Day 7, increased through to Day 9, and then decreased through to Day 20, although with values higher than in healthy controls. There was no increase in inflammatory CD14+CD16+monocytes, nor in activated NK CD3-CD56+HLA-DR+ cells. Regarding serum cytokines, of the 17 pro-inflammatory cytokines studied, only low levels of MCP1/CCL2 were found on Days 7–9. This case is interesting since there are very few studies on patients with mild infections and because IgM and IgG antibodies, antibody secreting B cells, CD4 TFH cells, and activated cytotoxic CD8 cells were shown to be circulating before resolution of the symptoms.

Ong et al. compared the blood transcriptional profile of three patients in early phases of Infection, one of whom evolved to a severe disease with 10 healthy volunteers. The main findings in the patient who progressed to severe disease was that only IL-1A and IL-1B preceded the nadir of the respiratory function, and that the expression of most inflammatory genes, particularly IL-6, IL-2, TNF- $\alpha$ , and IFNA1/13, peaked thereafter. Also, in this patient, transcripts associated with HLA, CD4, and CD8 T cell activation were diminished, while in the other two patients, who did not progress to severe disease, the transcription profile was comparable to that of healthy controls. The authors suggest that in the first case the decreased T cell activation may have helped the inflammatory response by the IL-1 pathway, while in the other two cases the low inflammatory response allowed a moderate T cell response.

## 6.2 Dynamics of Innate and Adaptive Response due to Effect of Age

One of the risk factors most strongly associated with severe COVID-19 and death is advanced age. Immunosenescence present in the elderly

which affects innate immunity but mainly T cell-dependent adaptive responses [48,49]. In addition, experimental evidence suggests that elderly mice have increased levels of proinflammatory cytokines and that their alveolar macrophages are refractory to activation by IFN- $\gamma$  [50]. This finding is useful since the protective response that eliminates the virus depends on cytotoxic CD8 cells and Th1 responses, with IFN- $\gamma$  playing an important role in both responses, as demonstrated in SARS and MERS [49].

Increased susceptibility in the elderly followed by presentation of severe COVID-19 forms contrasts with the lower frequency of these forms in children and young adults. Ludvigsson reviewed 45 publications on COVID-19 and found that 1–5% of the patients are children who, although they present with fever and respiratory symptoms, experience milder symptoms and among whom death was extremely rare. The increase in inflammatory markers and lymphocytopenia were also less common in children [51]. Brodin postulated the following three explanations for the milder COVID-19 presentation in children than aging adult [52].

Extensive studies reveal that the immune response is qualitatively different in children and adults [53].

The simultaneous presence of other viruses in the mucosa of the respiratory tract, common in children, could limit the growth of SARS-CoV-2 by direct virus-to-virus competition.

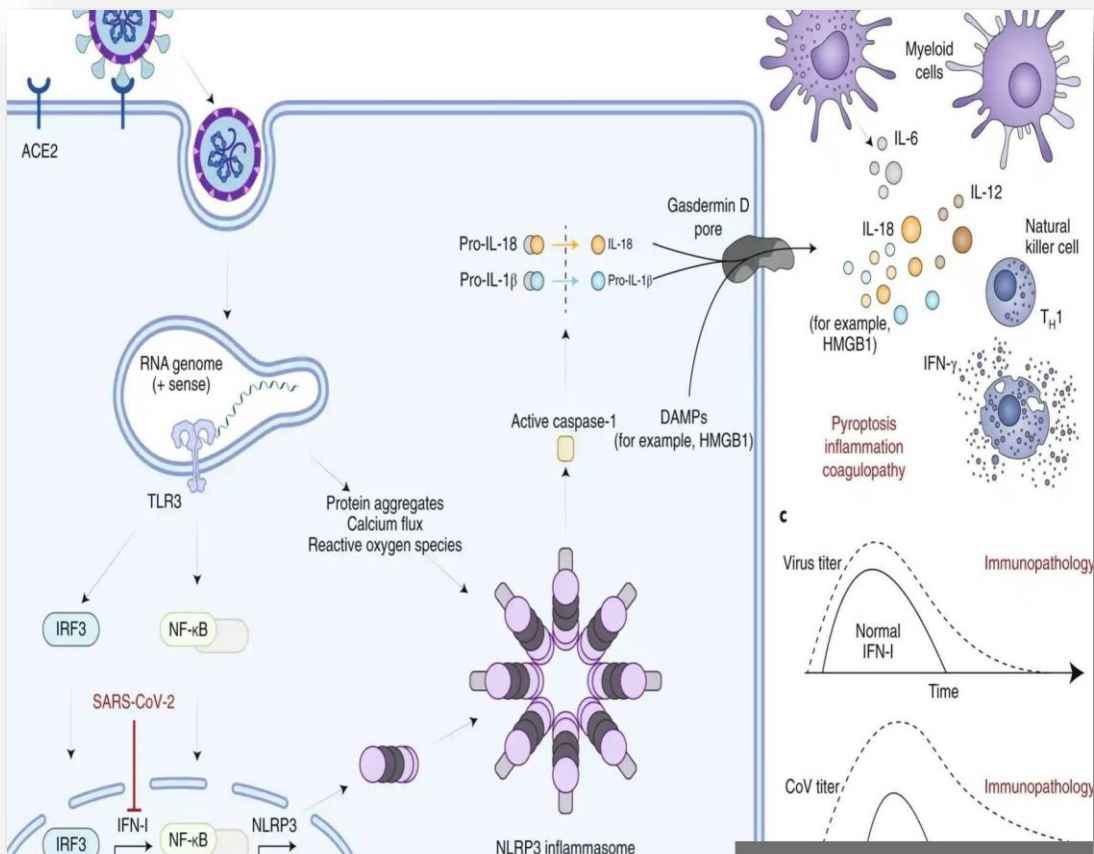
Elderly individuals experience dynamic expression of pro-inflammatory genes, which most of these genes peaked after the nadir of respiratory function brings in cytokine storm, According to research data of Eugenia et al. [6] which reveals the possibility that the interleukin-1 (IL-1) pathway is one of the key suitable correlate contributing to severe respiratory disease in Sars-Cov-2 infection. In addition, the attenuated cytokine expression associated with mild infection could also delay T cell immunity against SARS-CoV-2, which prolongs infection; this suggests the possibility that its infection without fever (afebrile) and undifferentiated COVID-19 cases may drive virus spread in the community [6].

The changes observed particularly affect the elderly persons with immune-senescence and persons with previous ailment immune

derangement. Example an index case 1, 2,3 study of a 66, 37, and 38 years old man and his sons by Eugenia et al. [6]. These findings revealed the dynamics shown as first, Case 1 of the 66years old man who had reduced activation of adaptive immune genes, which unleashed the toll-like receptor TLR-mediated pro-inflammatory response which affirms an experimental study that found that reduced T cell activation potentiates TLR-mediated inflammation in a positive feedback loop (Kim et al., 2007). Second and alternatively, increased expression of pro-inflammatory mediators in Case 1 could have led to recruitment of CD4+ and CD8+ T cells from the peripheral blood to sites of infection and the draining lymph nodes. That could have led to the mostly negative RT-PCR finding in the throat swabs from Case 1. In contrast, Case 2 of 37 years and Case 3 of 38 years old sons had lower pro-inflammatory responses with elicited mild symptoms and more attenuated T cell activation. Case 2 reported mild sore throat and cough that

started 3 days earlier, even before onset of symptoms he was afebrile (no fever) throughout the period of isolation, He did not develop lower respiratory tract complications, but throat swabs were consistently RT-PCR positive for SARS-CoV-2 until 23 days post illness onset and his cough resolved 10 days before SARS-CoV-2 real time polymerase chain reaction test (RT-PCR) became negative.

However, with an attenuated T cell response, SARS CoV-2 became prolonged as shown by the consistent viral RT-PCR positivity that lasted for nearly a month. In either case, our data indicates an important role of T cells in COVID-19. Defining the role of T cells in either the pathogenesis of severe COVID-19 or prolonged SARS CoV-2 infection should thus be a priority, as the understanding of this would impact case management and virus transmission control, respectively [6].



**Fig. 4. Illustrative Diagram of the Dynamics of innate and adaptive immune response to SARS-CoV-2 in human [38]**

The treatment with ACE2 inhibitors and angiotensin receptors blockers, a common procedure in hypertensive adults, up-regulates ACE2 expression, increasing susceptibility to SARS-CoV-2 infection. These theoretical possibilities require more clinical and experimental validation.

## 7. LIMITATIONS OF ADAPTIVE AND INNATE IMMUNE RESPONSE TO SARS-CoV-2 IN HUMAN BEINGS

Generally, viruses including coronavirus have number of avoidance ways from attack by immune system cells to better survive and infect host cells [43]. The strategy is applied to various processes, their point of entering the cell, when it has entered host cell. During the recognition process, this virus avoidance strategy is achieved through the development of Immuno-evasion mechanisms that mimics host cell system characteristics as follows.

### 7.1 Immuno-evasion Strategies of Coronaviruses SARS-CoV-2 against Human Immune Response

- The formation of double vesicles on the outside of the cell which causes shield recognition of cytosolic PRRs to dsRNA as an intermediate product of replication virus [44].
- Limitation of immune response activity with non-structural group of proteins (nsps) of SARS-CoV-2.
- Blocking interferons (INF) activity with (Nsp1) from SARS-CoV-2
- SARS-CoV-2 has 8 non-structural groups of proteins (Nsp) that can avoid immune system attack by blocking interferons (INF). Example non-structural group of proteins (Nsp1) from SARS-CoV can suppress the work of INF- $\alpha$  through host translational machinery inactivation, RNA-Host degradation and inhibition of phosphorylation of STAT1. The mechanism could cause INF- $\alpha$  failure to induce replication and dissemination of viruses at an early stage and leads to increased severity of disease [54].
- SARS-CoV-2 avoidance of PRRs recognition through mimicking formation and modification of its viral RNAs cap to resemble host cell RNA using nsp 14 and 16.
- The composition of the viral RNA genome including SARS-CoV has a 5' cap less than the host cell RNA for immune system cells to easily recognize its presence and induce an immune response. To avoid this, the virus mimics its host capping machinery using nsp 14 which initiates cap formation, and modifying the cap of viral RNAs by nsp 16 so that RNA viral seems similar to host cell RNA and avoids any PRRs recognition [54].
- Non-structural proteins (nsp) 3 & 5 from SARS-CoV-2 Promotes cytokine expression and cleavage of viral polyprotein.
- Other non-structural proteins from coronavirus that also have the ability to prevent this virus from immune responses are nsp3 that encoded two functional proteins, macrodomains and PLpro (cleavage of nsps). These proteins are employed as actors in the evading of SARS-CoV-2 from immune response-induced viruses. This possibility was supported by Fehr et al. in their in vivo study in BALB/c mice that were infected by SARS-CoV-lacking macrodomains. The findings of this study revealed that although there was an increase in expression of type I IFN, ISG15, CXCL10 and the proinflammatory cytokines IL-6 and TNF, followed by significantly higher survival, there was no lung pathology development in the mice. The finding is closely similar to other studies conducted in mice demonstrating a lack of deubiquitinating enzyme (DUB) activity in MERS-CoV. DUB is another role of PLpro to help coronavirus evade attack from a host's immune response by antagonizing the IFN response. From these findings, we hypothesized that the decline in function of the two proteins may lead to the direct introduction and sticking of immune troops to continuously infected cells and prevented the replication of the virus and the life cycle.
- Non-structural protein 9, (nsp9)  
It's an RNA binding protein phosphatase from Sars-Cov-2  
It strengthens its binding to host cells.
- Non-structural protein 12 (nsp12) of Sars-Cov-2 is a Replication enzyme.  
It's an RNA-dependent RNA polymerase that facilitates massive Sars-Cov-2 replication in the human host cell that are not interrupted by immune response.

- Non-structural protein (nsp 7/8) complex Processivity clamp for RNA polymerase by arms hexadecameric complex.
- In addition to using nonstructural proteins, SARS-CoV could utilize its protein accessories to avoid immune responses. For example the gene segment located on ORF3b of this virus has the ability to antagonize the INF signaling pathway and cause inhibition of the effector cell activation cascade for eradication and inhibition of viral replication [55].
- The protein encoded in ORF6 can inhibit JAK-STAT signaling pathway by binding to karyopherin- $\alpha$ 2, and tethers karyopherin- $\beta$ 1 on internal membranes to lead to blocking nuclear translocation of the transcription factor STAT1 [36]
- Impaired Interferon (IFN) production and function of host innate immune cells during SARS-CoV-2 infection.
- Leucopenia and lymphopenia sets in due to overproduction of cytokines (interleukin 6, 10 etc).
- Decrease transcription of natural genes encoding for production of immune regulatory and killer cells, (CD4+, CD8-, NK-FB)
- Programmed cell death of immune memory cells [38].
- Asymptomatic characteristics: Patient does not promptly show symptoms example intestinal symptoms like diarrhea that were evident in other coronavirus infections. Patients are recommended to be quarantined to prevent community Spread.
- SARS-CoV-2 disease has had a large negative impact on the environment and the society at large due to increased spread of the disease. Their invading and immune suppressing mechanisms in human are factors contributing to its infection severity [56-61].

## 8. CONCLUSIONS

The acute immune response to SARS CoV2 infection is dynamic, and these dynamics must be taken into account to understand the pathogenesis of COVID19 and determine the virus's most restrictive mechanism on the human immune response during infection. Case studies reviewed with data from human subjects 1, 2, and 3 shows that T cells play an important role in COVID19. Defining the role of T cells in the pathogenesis of acute severe COVID19 or SARS CoV2 infection in the long term should be a

priority, as understanding this will affect case management and control of virus transmission, respectively. Coronavirus (SARS CoV2) has a unique and complete composition. The immune avoidance component is the limiting factor, which causes the immune response to restrict it, so that it can evade recognition by the immune system. This leads to severe infection and death of the human host. The restriction mechanism imposed by the virus on the human immune response during the infection process is a huge challenge, and continuous research is needed to overcome it.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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