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# The COVID-19 Summary: Immunological Facts and Figures

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## ABSTRACT

The recent Coronavirus disease(COVID-19) has disrupted health as well as economic status throughout the globe. In December 2019, a sudden outbreak of pneumonia originating from the Wuhan city of Hubei province, China, turned into the COVID-19 pandemic worldwide. The infectious agent was later identified and characterised as being part of the Coronavirus family and was named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy. From several pieces of evidence, major similarities with the genome of bat CoVs, the origin of the virus was hypothesized to be zoonotic. Individuals affected by COVID-19 usually show common symptoms, including fever, dry cough, dyspnoea, hypoxemia, and pneumonia. Recent studies have revealed the role of the immune system in the pathogenesis of COVID-19 as the virus induces not only the host innate immunity but also impairs adaptive immunity and induces an uncontrolled inflammatory response, leading to disruption of normal immune homeostasis, tissue damage, and finally death by respiratory failure. In this chapter, it discusses the immunopathogenesis of COVID-19. Up to date, there are no such appropriate treatments with proven efficacy available for COVID-19. Proper understanding of the involvement of the immune system in pathogenesis is important to designing an effective therapy against the infection.

***Keywords:*** *COVID-19; Pathogenesis; Innate and Adaptive Immunity; Immune Dysregulations; Lymphopenia; Leukocytosis; Macrophage's Response; Cytokine Storm; Silent Hypoxia*

## INTRODUCTION

In December 2019, a sudden outbreak of pneumonia broke out in the city of Wuhan in the Hubei province of China. The infectious agent was soon identified as a member of the Coronavirus family. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the name given by the International Committee on Taxonomy to the deadly coronavirus stains. Interestingly, the outbreak was a continuation of a similar incidence in 2002-2003 in some parts of the world (Cherry, 2004). Later, on February 11, 2020, the World Health Organization (WHO) finally named the disease as COVID-19, short for "CoronaVirus Disease 2019" (Sun *et al.*, 2020).

The source of COVID-19 is still controversial. Although various pieces of evidence are found that support the zoonotic origin of the virus, probably from the wildlife food market in the Wuhan district of China (Wassenaar & Zou, 2020). However, whole-genome sequencing of SARS-CoV-2 revealed many more similarities with the genome of a virus harboured in the bat species Rhinolophus affinis (Li *et al.*, 2021).

## LITERATURE REVIEW

### The Coronavirus

Viruses are sub-microscopic particles that have the capacity to infect animals, plants, and even bacteria. They are found in every ecosystem on Earth. Coronaviruses are characterised as a diverse family of enveloped, positive-sense,single-stranded RNA viruses. The family is so named because of the large spike protein molecules that are present on the outer surface of the virus, offering a crown-like structure to the virion. The genome of the coronavirus family of the order Nidovirales is the largest

genome found among RNA viruses known till date (Gorbalenya *et al*., 2006). Their host range includes wildlife animals such as avians such as bats and mammals such as camels, pigs, and humans (Damas *et al.*, 2020).

**Structure and genomic characteristics of SARS-CoV-2**

SARS-CoV-2, the responsible viral pathogen for COVID-19 is an enveloped, single-stranded, positive-sense RNA virus. They are spherical in shape, with a diameter of 60-140 nm. The virus particle is made up of roughly four structural proteins, including Nucleocapsid protein (N), Envelope protein (E), Spike proteins (S) and Membrane protein (M), [Figure 1]. Spike proteins (S) are the outermost proteins that protrude from the outer fatty layer, so-called envelope, and are involved in the binding of the virus with the host cell receptor. The envelope proteins (E) and membrane proteins (M) are inserted into the lipidic envelope. Nucleocapsid protein (N) is the only protein present inside the virion that associates with the genomic RNA through electrostatic interaction. The functions of each structural protein are summarized in [Table 1]. (Bhardwaj *et al.*, 2022).

***Table 1: Structural proteins encoded by SARS-CoV-2 genome and their functions***

| Structural protein | Function |
|---|---|
| N protein | •Impairs IRF3 phosphorylation and nuclear translocation<br>•Prevents STAT1/STAT2 phosphorylation<br>•Prevents inhibition of viral mRNA translation<br>•Prevents GSDMD cleavage by caspase-1<br>•Disassembles and prevents formation of stress granules |
| E protein | •Forms an ion channel and participates in virion assembly |
| M protein | •Essential for the incorporation of viral components during virion assembly<br>•Impairs MAVS self-association and association with SNX8 |
| S protein | •Binds to the host receptor ACE2 and mediates fusion and entry |

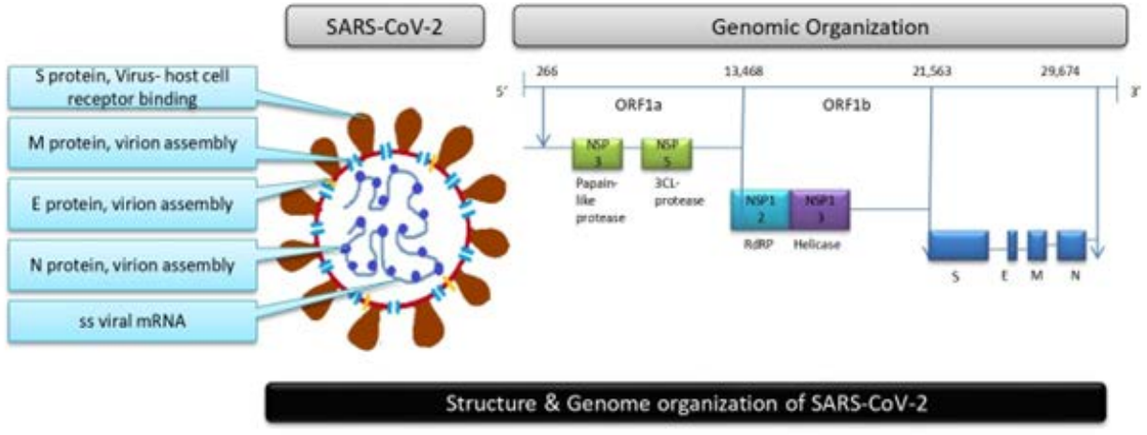


***Figure 1: Structure and Genome organization of SARS-CoV-2***

SARS-CoV-2 has shown genomic similarities with SARS-CoV and thereby is placed under the family Coronaviridae, order Nidovirales, genus Beta (β) coronavirus and subgenus Sarbecovirus. The +ve ssRNA genome of SARS-CoV-2 is about 26-32Kbp long. The genome comprises 12 open reading frames (ORFs) at the 5′ end of the viral genome. Two overlapping ORFs, 1a and 1b, are present, occupying approximately two-thirds of the genome and encoding the RNA polymerase and other non-structural proteins of the virus. Other structural proteins are encoded by the remaining one-third of its genome, which runs from the 5′ to the 3′ terminal (Gómez *et al.*, 2021). Interestingly, as the SARS-CoV-

2 and other RNA viruses have demonstrated, the host immune system can eventually be escaped with potential drug resistance due to mutation. For example, the genes encoding the spike protein and RNA dependent RNA polymerase are major hotspots of mutation as conferred in such viruses (Pachetti *et al.*, 2020).

**Different types of Coronavirus infection-**

Among the seven coronaviruses identified, SARS-CoV-2 is the most common cause of human infection. The other six coronaviruses include SARS-CoV, NL63, MERS-CoV, HKU1, OC43, 229E, among which SARS-CoV and MERS-CoV cause various life-threatening respiratory diseases, whereas the others cause mild symptoms(Bhardwaj *et al*., 2022).

**Table 2: Different CoVs illnesses**

| **Human coronavirus** | **Illness** |
|---|---|
| SARS-CoV-2 | COVID-19 |
| SARS-CoV | Severe Acute Respiratory Syndrome (SARS) |
| MERS-CoV | Middle East Respiratory Syndrome(MERS) |
| HCoV-NL63 | Mild symptoms |
| HCoV-229E | |
| HCoV-OC43 | |
| HKU1 | |

The novel coronavirus (SARS-CoV-2), SARS-CoV (2002), and MERS-CoV, are major pathogens belonging to the family of Coronaviridae that primarily target the human respiratory system. In 2002, an epidemic caused by SARS-CoV, another beta coronavirus, began in South China. In 2012, the first case of MERS-CoV was reported in Saudi Arabia, whereas, in December 2019, COVID-19 infection emerged from Wuhan, China. The SARS-CoV like coronavirus derived from bats shares 88% sequence similarity with SARS-CoV-2, whereas the MERS-CoV viruses are 50% identical to the novel SARS-CoV-2 falling under the genus β-CoV(Abdelrahman, Li & Wang,2020).

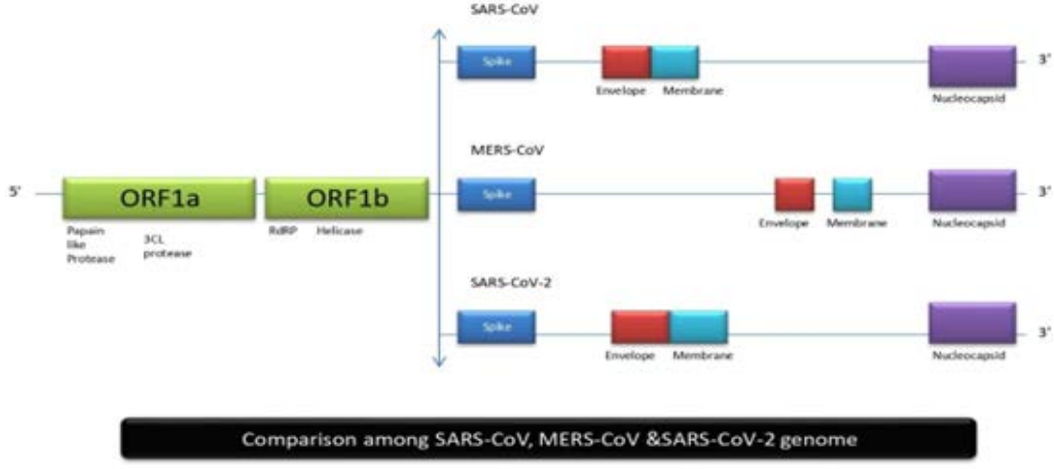


***Figure 2: Comparison among SARS-CoV, MERS-CoV& SARS-CoV-2 genome***

Notably, slight although significant differences can be found in terms of sequence, nucleotide number, gene order, and expression method among SARS-CoV, MERS-CoV, and SARS-CoV-2 falling under the same serogroup. For example, genes encoding the S protein, NSP(non-structural protein)2, NSP(non-structural protein)3, and receptor-binding domain (RBD) are prone to a few amino acid substitutions as reported in the novel SARS-CoV-2. The strain also showed significantly higher binding efficiency (10–20 times) of ACE2 and S protein in several studies as compared to the

previously known SARS-CoV. Therefore, the enhanced pathogenicity is believed to be due to the series of mutations resulting in higher binding efficiency to host cells as reported in recent studies (Zheng & Song, 2020; Nguyen *et al.*,2020). Notably, the MERS-CoV binds specifically to the Dipeptidyl Peptidase 4 (DPP4) receptor to gain access to its host cells, whereas the SARS-CoV-2, similar to the SARS-CoV, exploits the Angiotensin-converting enzyme 2 (ACE2) receptor (Meyerholz, Lambertz & McCray Jr, 2016).

**Life Cycle of Coronavirus (SARS-CoV-2)-**

To understand the pathogenesis of a virus, a clear concept of its life cycle is necessary. Like other viruses, the novel coronavirus (SARS-CoV-2) also follows six general steps to complete its life cycle: attachment, penetration, uncoating, gene expression and replication, assembly and release [Figure-3]. A clear understanding of the life cycle of SARS-CoV-2 will help to understand how the virus elicits immune responses in the host body, and thereby the immunopathogenesis of SARS-CoV-2 will be dived into.

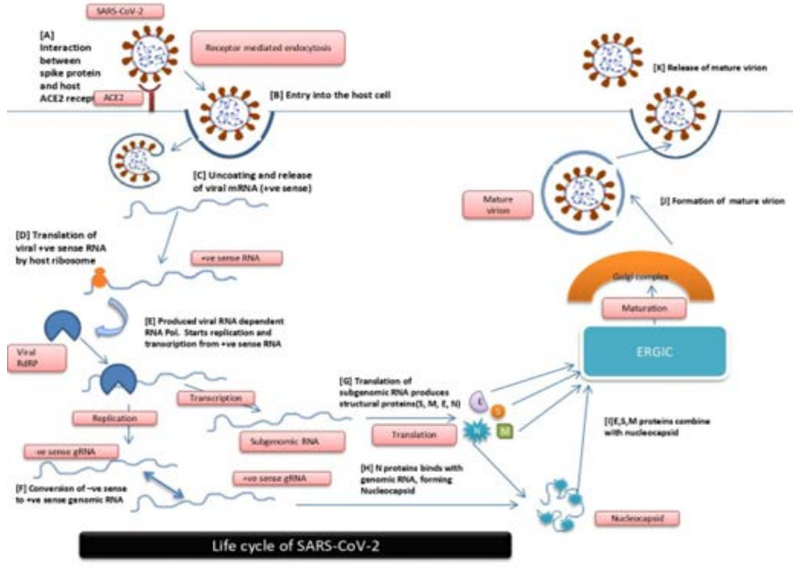


***Figure 3: Life cycle of SARS-CoV-2***

**Entry of virus:**

As stated earlier, SARS-CoV-2 infects the respiratory system by reaching the lungs via the naso-oral cavity. In the respiratory tract, it mainly invades mucus-producing ciliated epithelial cell lines or endothelial cells of the lungs. The primary virion-cell surface attachment is promoted by the mammalian cell attachment factor such as heparan sulphate. The entry of the virus is accomplished by the interaction between the viral spike protein's receptor-binding domain (RBD) and the host cell receptor Angiotensin-converting enzyme-2 (ACE2) (Clausen *et al.*, 2020). Angiotensin-Converting Enzyme 2 (ACE-2) is a type of membrane receptor that is expressed in almost all tissues of the human body, especially in capillary-rich organs such as kidneys, lungs etc.

The spike protein of the virus consists of two domains, S1 and S2. The receptor-binding domain (RBD) is present on the S1 subunit and, therefore, the S1 subunit binds to the ACE2 receptor. Hence, this subunit is involved in the determination of tissue tropism. The fusogenic activity of the virus-cell membrane is governed by two tandem domains, heptad repeats (HR1,2), that are present in the S2 region of the S protein. The interaction between the spike protein and the host receptor changes the conformation of the spike protein, followed by its activation and proteolytic cleavage at the S2 subunit. The processing includes priming of S1 and S2 subunits (those are non-covalently attached) followed by cleavage within the S2 subunit. These processing steps are manifested by the host's membrane protease or by the enzymes at the low pH of the endosome (in the case of endosome mediated entry), resulting in membrane fusion and thereby facilitating virus entry inside the cell (Benton *et al.*, 2020).

Once the virus reaches the host cell via membrane fusion, the +ve sense ssRNA genome is released into the cytoplasmic compartment, finishing the uncoating step of infection.

**Gene expression and replication:**

As SARS-CoV-2 contains a positive-sense RNA molecule, it can directly be used as a translational template by host cellular machinery. Therefore, after uncoating of the viral genome in the host cell cytoplasm, the virus hacks host translational machinery and starts expressing the viral mRNA. The translation of ORF-1a and ORF-1b results in the expression of two large polyproteins, pp1a and pp1b, respectively. These polyproteins are further cleaved into 16 non-structural proteins (NSP1-16) by three distinct functional proteases, thereby forming the viral RNA-dependent RNA polymerase core complex and other accessory proteins for virus assembly. An uninterrupted replication-transcription event results in the formation of sub-genomic mRNAs. Those are eventually translated into numerous structural and accessory proteins thereafter (Beig Parikhani *et al.*, 2021).

**Assembly and release:**

In post-synthesis, the resulting accumulation of structural proteins, such as the E proteins, is incorporated into the rough endoplasmic reticulum or Golgi membrane. The nucleocapsid is formed by the combination of +vessRNA with the capsid protein (N) and the subsequent assembled virus particles pass through the ER-Golgi Intermediate Compartment (ERGIC) and are finally matured for release. At this stage, particle-loaded vesicles are fused with the cell membrane. The new virions are ready to infect the neighbouring healthy cells. They are also released into the surrounding environment via respiratory droplets as infecting particles (Beig Parikhani *et al.*, 2021).

**Pathogenesis of COVID-19:**

SARS-CoV-2 reaches the lungs through the naso-oral cavity after inhalation of bioaerosols. It enters the epithelial cell line through the ACE2 receptor. The infection of SARS-CoV-2 can be divided into two stages. First, one to two days is the asymptomatic stage when the virus enters and multiplies in the cells of the upper respiratory tract. Thereafter, the virus begins to move through the naso-oral tracks towards the lower respiratory tract. As the virus first infects the upper respiratory tract, a mucus immune response starts to work, but the intensity of the viral infection becomes so high that it fails to eliminate the infection. However, when a virus particle reaches the lower respiratory tract, it provokes a strong immune response [Figure-4]. As discussed earlier, after invasion into the epithelial cell line, viral genome uncoating occurs, followed by gene expression and replication, thereby commencing the infection (Shah *et al.*, 2020).

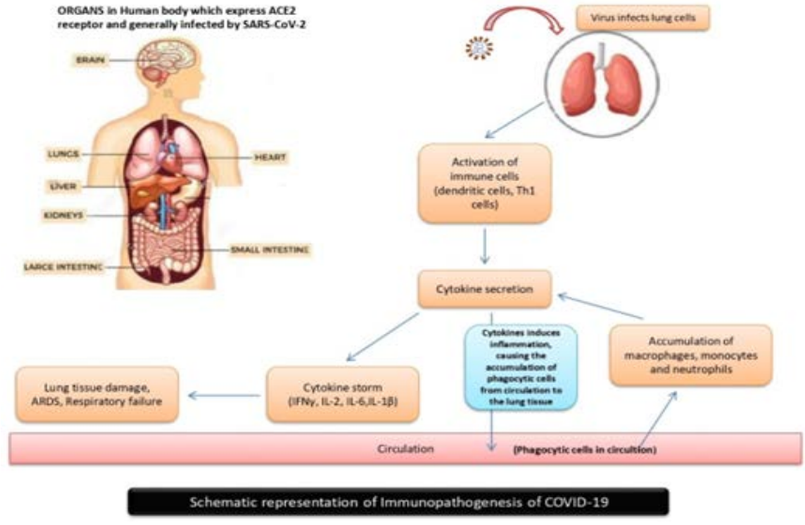


***Figure 4: Schematic representation of Immunopathogenesis of COVID-19***

**Innate immunity**

Virus infection first stimulates the innate immune system into the host. Pathogen associated molecular patterns (PAMP) are recognized by the pattern recognition receptor (PRR), present on the innate immune cells and triggers their activation. In the endosome, there are specific types of pattern recognition receptors (PRR) that associates with SARS-CoV-2 viral genomic ssRNA, ds intermediate RNA formed during viral replication, viral spike protein, viral membrane protein and other associated viral proteins. These PAMP molecule includes Toll-like receptors (TLR3, TLR8, TLR7, and TLR9) or the cytosolic RNA sensor, RIG-I/MDA5 or the secretory type PRR like Mannose-binding lectin (MBL) and C-reactive protein (CRP) (Chatterjee, Saha & Munoz, 2020). This recognition activates downstream cascade molecules and thereby provoking the transcription of type1 interferon molecules and other proinflammatory cytokines, especially IL-6. Notably, a potent innate immune response against viral infection and effective adaptive immune response is induced by Interferon (IFN) type I essentially mediatedby the JAK-STAT pathway. The viral replication is thereby suppressed due to the accumulation of type I IFN resulting phagocytosis of antigens by the macrophages (Bouayad, 2020).

Strikingly the virus can survive within the host cell in the case of patients with disorder in JAK-STAT signalling pathway or any blockage in IFN production or even in the case of altered expression of macrophages. SARS-CoV-2 usually goes through these types of mechanisms to evade the host immune system. Usually, suppression of antiviral type 1 IFN response attributes in evasion of host innate immune response by the SARS-CoV-2. It has been shown that several protein-mediated mechanisms are involved that behave in antagonistic ways to the expression of type1 IFN.

- SARS-CoV-2 shields viral mRNA from the cellular sensory molecules to prevent IFN production.
- SARS-CoV-2 prevented IFN production by disrupting the stimulator of IFN genes.

Thus, the virus infection evades innate immune response by suppressing type1 IFN activity but the infection triggers a robust production of pro-inflammatory cytokines that leads to an influx of neutrophil and monocytes.

**Adaptive immunity**

Adaptive immune responses are mainly regulated by two types of lymphocyte cells: T lymphocyte and B lymphocyte. The antigen presenting cells (APCs) majorly regulate the T-cell response. In the case of viral infection, viral polypeptides and mRNA act as endogenous antigens and, after being processed, they will be presented towards $T_H$ cells by MHC class I molecules of APCs. According to their presentation, CD8+ cytotoxic T cells and antibodies secreted by activated B cells will eventually act on the elimination of pathogens (Owen, Punt & Stranford, 2013).

**Antigen presentation in SARS-CoV-2**

In hosts such as humans, the Major Histocompatibility Complex (MHC) is known as the Human Leukocyte Antigen (HLA) complex. This system is controlled by genes located on chromosome 6, encoding cell surface molecules specialized to present antigenic peptides to the $T_H$ cell receptor. With the binding of antigen, $T_H$ cells get activated and they produce cytokines, thereby triggering the cytotoxic effect of $T_C$ cells. However, in some cases of SARS-CoV-2, the involvement of MHC class 2 molecules has also been documented. Alleles of HLA such as HLA-DRB1*1202, HLA-B*0703, HLA-B*4601 and HLA-Cw*0801 are found to be more prone to be susceptible to coronavirus whereas alleles including HLA-Cw1502, HLA-DR0301 and HLA*0201 are involved protection against SARS infection (Khosroshahi *et al.*, 2021).

On the other hand, neutralizing antibodies, mainly IgG and IgM are produced in the B-cell mediated humoral immune response. The viral spike (S) and nucleocapsid (N) proteins are the sole target for most of the circulating antibodies in the case of CoVs infection. Several studies performed on patients with COVID-19 haverevealed the antibody level in their serum by using magnetic chemiluminescence

enzyme immunoassay (MCLIA) [Figure-5]. The studies revealed IgM happens to be the first isotype to be detected in the serum followed by followed by IgA after 2-3 weeks of onset of symptoms. This declines gradually with the rise in level of IgG antibodies that can be detected even after several months post symptom onset (PSO) (Wu *et al*., 2021).

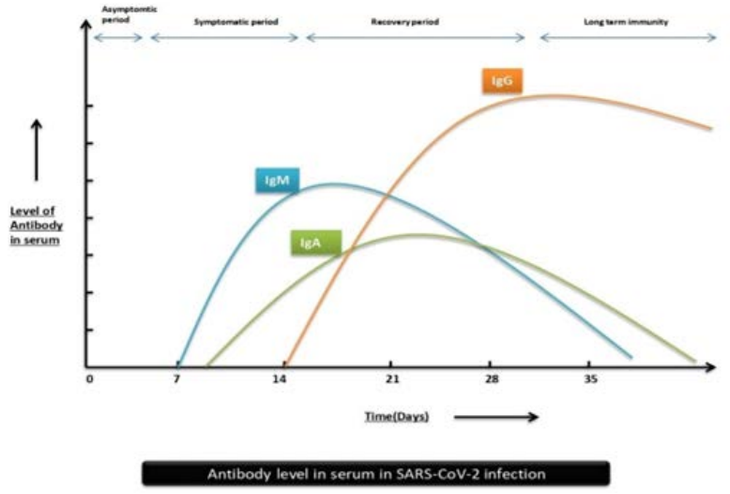


***Figure 5: Antibody level in serum in SARS-CoV-2 infection***

**Dysregulation of immune cells/molecules in COVID-19:**

SARS-CoV-2 infection destroys the intervening regulation between various immune cells and molecules, thereby leading to damage to immune homeostasis [Figure-6]. The SARS-CoV-2 infection stimulates an unrestrained innate immune response resulting in the production of an excess amount of pro-inflammatory cytokines, IFN-γ, macrophage colony-stimulating factor (MCSF) etc. that are associated with disease severity, causing tissue damage in the lungs and resulting respiratory failure. The common immune dysregulation associated with COVID-19 infection includes lymphopenia, leukocytosis, cytokine storm, ARDS (silent hypoxemia), and changes in macrophage behaviour, as described in the following section [Table-3].

***Table 3: Responses of various immune cells during COVID-19:***

| Immune cells | Response to SARS-CoV-2 infection |
|---|---|
| Monocytes and Macrophages | • abundance of macrophages in the lungs<br>• Macrophages produce proinflammatory cytokines such as IL-2, IL-6, IL-7, IL-Iβ and TNF-α<br>•Delayed or supressed type 1 IFN response |
| Dendritic cells | • Produce excess amount proinflammatory cytokines and chemokines (TNF-α, IL-6, RANTES , IP-10, MCP-1, MIP-1α, CCR1, CCR3 and CCR5)<br>• Infection of dendritic cells with SARS-CoV-2 supresses MHC-I expression that causes further delay in the expression of IFN- α<br>• Increased expression of TRAIL(TNF related apoptosis inducing ligand) which leads to apoptosis of lymphocytes on their interaction with<br>Dendritic cells, thereby adaptive immunity gets exhausted. |
| Natural killer cells | • SARS-CoV-2 infection depletes NK cell population<br>• High level of IL-6 cytokine during SARS-CoV-2 infection inhibits cytotoxicity of NK cells |

| | |
|---|---|
| Mast cell | •SARS-CoV-2 infection induces mast cells to secrete proinflammatory cytokines like IL -1, IL-3 and IL-6, histamine and protease.<br>• Mast cells upregulate RAS activity in airways<br>• Mast cells secrete serine proteases. |
| Neutrophils | • Increased in number<br>• Increased neutrophil to lymphocyte ratio<br>• Increased NET release which leads to ARDS, thrombosis, coagulation and worst oxygenation conditions observed in COVID-19 patients |
| Eosinophil | • Gets depleted upon SARS-CoV-2 infection. |
| Basophil | • In severe COVID-19 patients number of basophils gets decreased. |
| T cell | • In SARS-CoV-2 infection the population of CD4+ T cells and CD8+ T cells get depleted, the state is called Lymphopenia. Therefore, the adaptive immune response b ecomes exhausted completely. |
| B cell | • Delayed antibody response. |

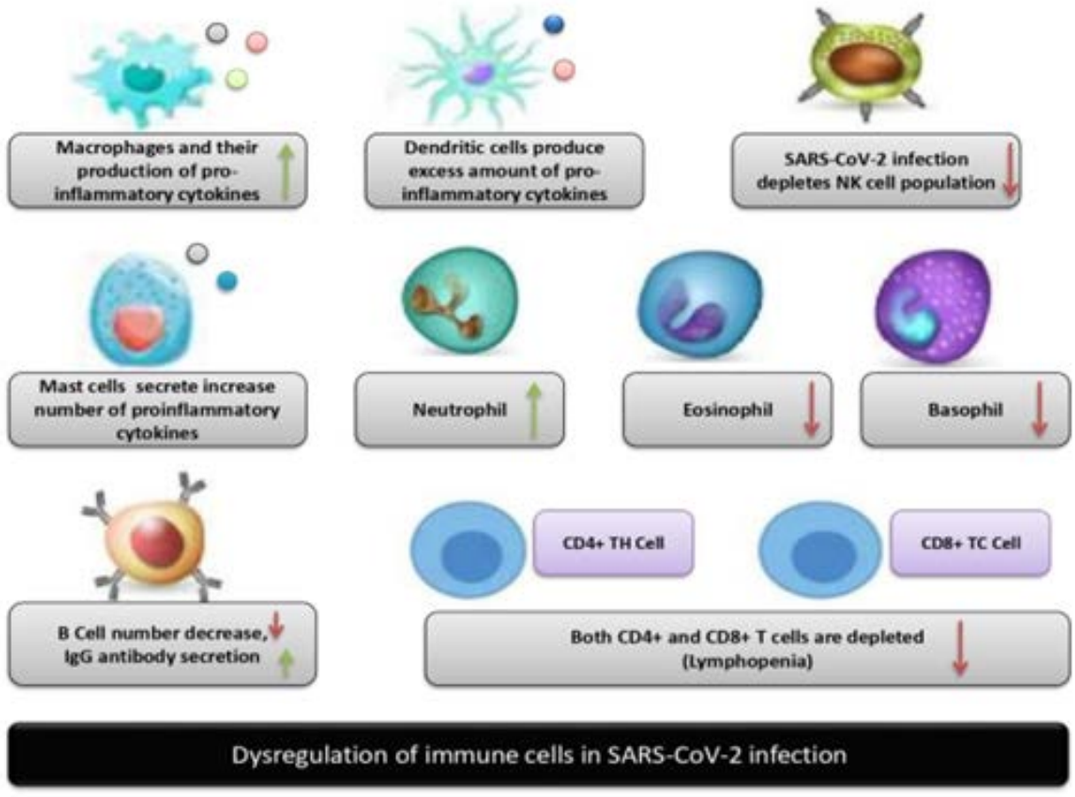


***Figure 6: Dysregulation of immune cells in SARS-CoV-2 infection***

**Lymphopenia:**

In severe cases of patients with COVID-19, lymphopenia is one of the major symptom observed among patients. The serious outcome involves significant reduction (<20%) of lymphocyte percentage in patient's serum [Figure-7]. Arguably the lymphocyte depletion in COVID-19 patients involves several potential mechanisms.

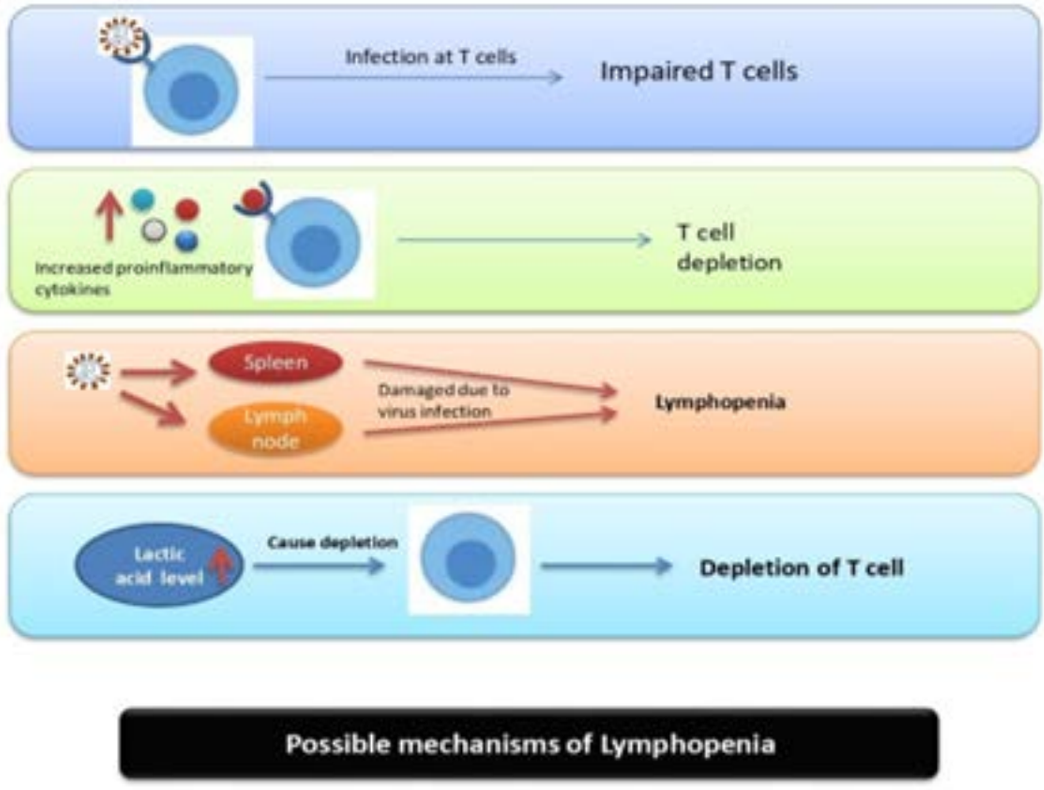


*Figure 7: Possible mechanisms of Lymphopenia*

(a) It is observed that level of proinflammatory cytokines (IL-6, IL-10 and TNF-α) in serum is inversely proportional with number of lymphocytes in peripheral blood.

(b) Notably the lymphatic organs including spleen and lymph node are directly destroyed by the process of spleen atrophy and necrosis of lymph node respectively by the SARS-CoV-2 virus inducing lymphopenia.

(c) Apoptosis of lymphocytes can be observed by upregulation of Fas expression in the cases of some COVID-19 patients.

(d) Interestingly, entry of SARS-CoV-2 into the lymphocytes and corresponding infection of T-cells and macrophages are often regulated by expression of ACE2 receptor essentially on the T-cells.

(e) The proliferation of lymphocytes is inhibited by increased level of lactic acid as detected in the blood of patients with severe COVID-19 (Yang *et al.*, 2020).

**Leukocytosis:**

The condition of excess accumulation of neutrophils in the blood of patients is known as neutrophilia. Strikingly, infection of secondary microbes leads to an increased level of neutrophils in the blood, often leading to an abnormal number of granulocytes (neutrophils) and monocytes. The presence of excess pro-inflammatory cytokines and impaired lymphocytes in patients with COVID-19 might be easily attributed to an abnormal number of granulocytes, especially neutrophils. Interestingly, the Neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio remained higher in the patients with COVID-19. Neutrophil upregulation in patients with COVID-19 is closely associated with lymphopenia where these cells provide the first line of defence by killing microbes via phagocytosis and degranulation. This often induces neutrophil recruitment to the tissue site where the infection has been initiated (Jimeno *et al.*, 2020).

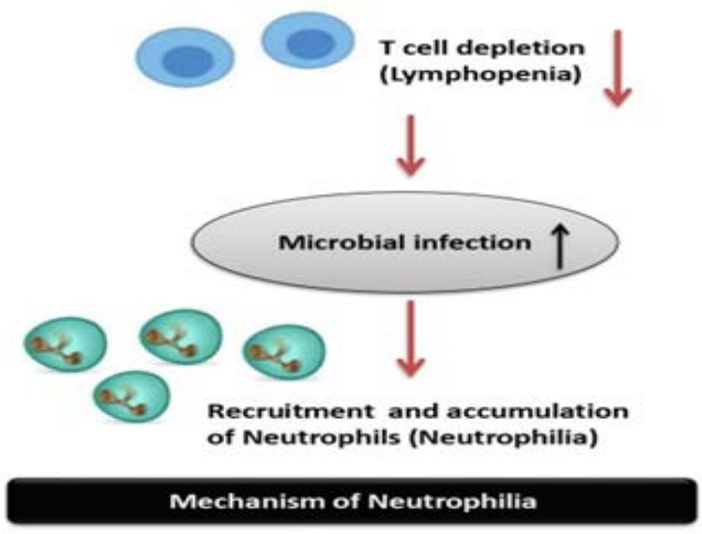


***Figure 8: Mechanism of Neutrophilia***

**Monocyte/Macrophage phenotypic changes:**

The macrophage activation syndrome is a dysregulated response to the cells, damaging the host in the case of SARS-CoV-2 infection. A profound alteration of activation status in the monocyte/macrophage system can be observed in patients. However, the absolute monocyte counts remain the same in severe COVID-19 cases. Additionally, higher numbers of inflammatory monocyte derived macrophages can be observed with significant depletion in tissue resistant alveolar macrophages. (Zhang *et al.*, 2021).

**Cytokine Storm:**

Cytokines are chemical mediators produced by several immune cells like innate macrophages, dendritic cells, NK cells, and T and B lymphocytes as an essential component of the inflammation reaction. Large amounts of pro-inflammatory cytokines can be detected in COVID-19 infection, causing an aggressive inflammatory response known as "cytokine storms". [Figure 9] Excessive inflammatory reaction events can be observed in patients with COVID-19, resulting in lung injury. The pro-inflammatory cytokines such as IL-6, IL-1β activates the signalling pathways, resulting in the elimination of infection by recruitment of leukocytes and a few plasma proteins to the infection sites, exerting effector function.

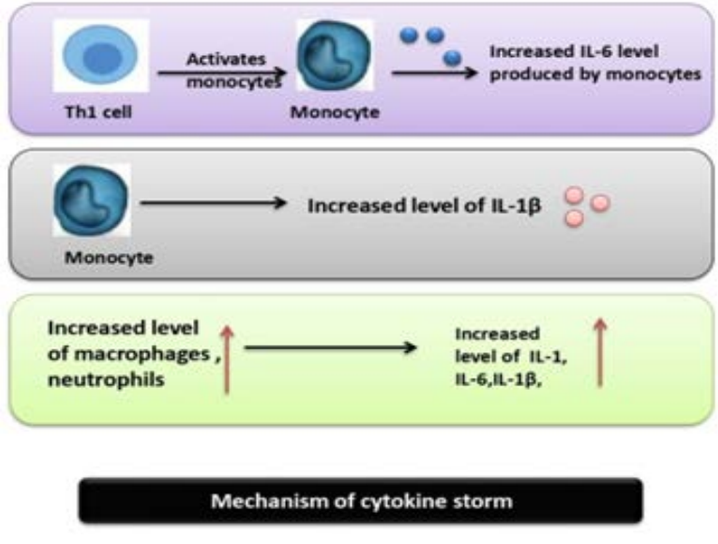


***Figure 9: Mechanism of cytokine storm***

Three types of the most important proinflammatory cytokines that are involved in the innate immune

response are IL-1, IL-6, and TNF-α, produced by tissue macrophages, mast cells, etc. The sudden increase in the cytokine's level results in the unchecked influx of various immune cells like neutrophils, T cells, and macrophages from the circulatory system to the infected tissue, which ultimately exhibits a number of consequences, including damage of the vascular barrier and capillary, diffuse alveolar damage, multi-organ failure, and finally leading to the death of patients (Ragab *et al.*, 2020).

**Silent Hypoxia:** Silent hypoxia is a critical condition where an individual has an alarmingly lower (~ 50-80%) oxygen saturation level than the expected value (>95%). However, the question might arise, why is this called "silent"? In normal hypoxia, the respiratory rate is elevated to the point where the condition is termed as dyspnea. But in cases of COVID-19 patients, the affected individual doesn't have any signs of distress even at the low oxygen saturation level. The underlying patho-mechanism behind this condition in SARS-CoV-2 infection is still under research. However, the prevalence of silent hypoxia in COVID-19 patients ranges from 20–40%.

Several investigations support that unrestrained induction of innate immunity leads to the production of a high level of inflammatory response, which ultimately results in tissue damage. Due to excessive lung tissue damage, alveolar air sacs collapse, resulting in a low oxygen supply in the blood.

Interestingly, the Hypoxia-inducible factor (HIF-1) is a dimeric transcription factor that acts as a master regulator of oxygen homeostasis in cells. The factor consists of two subunits of HIF-1α and HIF-1β. This factor is activated during conditions of reduced oxygen levels in patients. HIF-1α subunit has a potent effect on the expression of the ACE2 receptor gene. As stated earlier, ACE2 is the key receptor through which SARS-CoV-2 enters the host cell. Therefore, the hypoxic state has been found to stimulate the overexpression of the ACE2 receptor, thereby worsening COVID-19 infection that ultimately results in respiratory failure and death [Figure 10] (Rahman *et al.*, 2021).

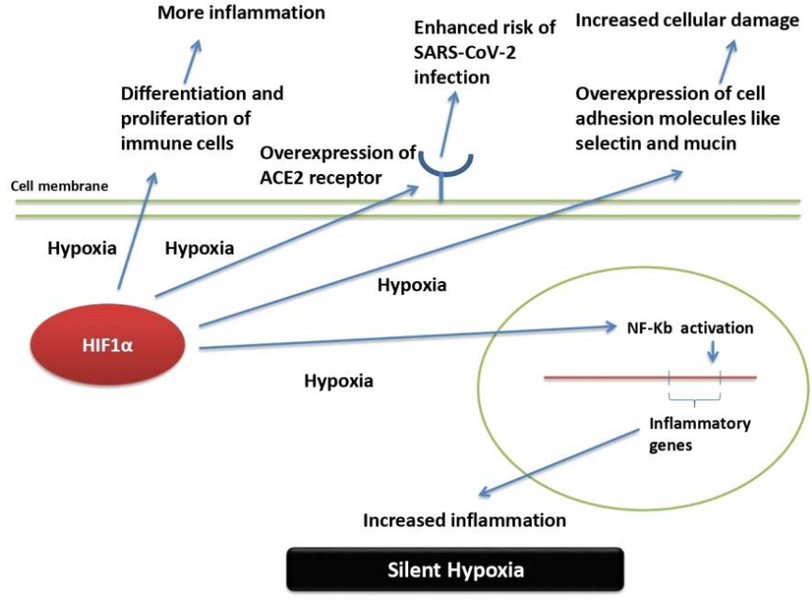


***Figure 10: Silent Hypoxia***

## CONCLUSION

After the sudden emergence of the SARS-CoV-2 virus in 2019, a lot of papers and publications have been made to clarify the interactions between the pathogen and the host during the infection process. A clear image of this complex interaction is truly necessary to design an effective strategy against the infection and to move the present status of immunotherapies one step forward. Exact information on the virus's life cycle, genetic features, and interaction with specific host cellular biomolecules is critical for understanding and identifying new antiviral targets, and thus designing new therapies.

Finally, after quite a long journey through the pandemic situation, the infection rate finally slowed down.

However, the information and the data are being documented by the interests of several groups of researchers, which will be translated into effective strategies and will be helpful for the world to combat future viral outbreaks.

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