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# COMPREHENSIVE REVIEW ON THE IMMUNITY STATUS OF THE HUMAN BODY WITH REFERENCE TO COVID-19

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## Abstract

*This condition is known as the severe acute respiratory syndrome. The respiratory infectious condition known as coronavirus disease 2019, sometimes known as COVID-19, is caused by coronavirus 2, which is also the name of the causal agent (SARS-CoV-2). The SARS-CoV-2 virus is most commonly transmitted by droplets floating in the air and through direct contact with persons who are afflicted. The symptoms of the disorder might range from none at all to a life-threatening illness, depending on the severity of the condition. The variability of this illness is one of its defining characteristics. To this day, not all of the factors that were related with the conclusion of COVID-19 have been precisely described in the way that they should have been. Previous study that was conducted on the relevance of infectious diseases served as the motivation for this new line of inquiry, which led to the identification of viral and host characteristics that were connected to clinical outcomes. The severity of COVID-19 is mostly dictated by characteristics related to the host, namely the cellular immunological responses that are exhibited by patients. People who have COVID-19 with a moderate severity and patients with severe COVID-19 who have improved have an immune response that is usual and can effectively eliminate the virus. Patients who were diagnosed with severe COVID-19 are showing continued signs of improvement. Patients who are suffering with a deadly form of COVID-19 will go through all three stages of the immune response: normal or hypofunction, hyperactivation, and anergy. The first stage is known as normal function or hypofunction. Due to the fact that they were unable to mount an effective defence against the viral infection, the patients ultimately passed away.*

**Keywords:** *immunity, human body, Covid -19*

## Introduction

The present epidemic of the coronavirus 2019 (COVID-19), which was produced by severe acute respiratory syndrome coronavirus 2, has resulted in a global health disaster on a scale that has never been seen before. This disaster has been brought about as a direct consequence of global travel (SARS-CoV-2). SARS-CoV-2 is often transmitted either via direct contact with infected individuals or by the exchange of droplets. The symptoms of the disorder can range from none at all to severe illness, with 10–20 percent of symptomatic persons being in a considerable risk of passing away from the ailment. The symptoms of the condition can be

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quite diverse. Critical diseases include things like acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulopathies, dysfunction, and multiple organ failure which can include problems with the heart, liver, kidneys, and brain. There is a connection between having comorbidities, being older, and having lower results. There is also a correlation between having poorer results and being male. When it comes to illnesses that are brought on by viral infections, both the viruses and the hosts have the potential to be contributors to the disease's heterogeneity. Studies have shown that SARS-CoV-2 has a limited genetic variety and a continuous evolution, both of which suggest that viral genetic diversity and evolution might contribute to the fatality and contagiousness of the disease. On the other hand, a significant connection does not appear to exist with the heterogeneity of COVID-19. Numerous researches have demonstrated that the intensity of the symptoms and the outcomes are closely tied to the immunological responses of the hosts. This connection is directly related to the severity of the symptoms and the results. "The innate immune system, which includes monocytes, granulocytes, dendritic cells (DCs), and natural killer (NK) cells, as well as the adaptive immune system, which includes T and B lymphocytes" are both required in order to build an efficient defence against SARS-CoV-2. Lymphopenia with a reduction in CD4+ and CD8+ T cells, lymphocyte activation and dysfunction, an increase in circulating neutrophils with the appearance of circulating neutrophil precursors, dysfunction of classical monocytes and loss of non-classical monocytes, reduced abundance and dysfunction of DCs and NK cells in patients with severe COVID-19. Patients with severe COVID-19 also have reduced abundance and dysfunction of DCs and NK cells. Patients who have a severe case of COVID-19 have been shown to have an increase in the number of circulating neutrophils, along with the appearance of circulating neutrophil precursors. There is an increase in the levels of inflammatory cytokines everywhere throughout the body, most noticeably interleukin IL-6 and IL-1 cytokines. This is due to the fact that the levels of these cytokines have been on the rise (29). On the other hand, the reaction of interferon is slower, and the levels of immunoglobulin G (IgG) and total antibodies are higher than normal. Instances of severe infections and sepsis are associated with a high prevalence of immune system diseases. These disorders can be separated from one another by the development of a high-grade inflammatory state that suppresses the immune system. There has been speculation about a mechanism for severe COVID-19 that is fairly comparable to this one. As there are now no specific antiviral drugs on the market, the immune response of the body is a crucial factor in defining the course of the disease and the outlook for recovery. As a consequence of this, a more in-depth understanding of the cellular immune response throughout the course of the illness, from very innocuous to possibly fatal, is required. The availability of COVID-19 is a prerequisite for the research and development of diagnostic markers as well as potential treatment options for COVID-19.

The activation of the antiviral immune response, the recruitment of antiviral immune cells, and the resolution of an infection caused by SARS-CoV-2 all need a highly coordinated cellular and molecular cascade. This is because SARS-CoV-2 infections are caused by the SARS coronavirus. These cascades help keep a careful balance between the elimination of viruses and the damage done to the immune system as a result of the infection. During an infection with a virus, a number of the body's innate immune recognition mechanisms work

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together to keep an eye out for viruses and create a defence against them (33). Using "cytokines (such as IL-1, IL-18, and IL-6)" chemokines, and type I/III IFN (34), the innate immune system is able to send out a rapid antiviral response in a matter of a few hours. This is possible because of the innate immune system's ability to send out type I/III IFN (such as CCL2 and CCL7). This reaction is being implemented with the goal of preventing the spread of viruses. After then, adaptive immunity kicks in and starts protecting the body. After an infection with a virus, T lymphocytes are primarily responsible for the majority of viral clearance, whereas humoral immunity is primarily responsible for the production of antibodies and the neutralisation of viruses. T lymphocytes are also responsible for the majority of the viral clearance. T lymphocytes are responsible for the removal of viruses by immediately disintegrating and destroying contaminated cells. In addition, T lymphocytes secrete cytokines in order to boost the immunological response of other T lymphocytes as well as other immunocompetent cells, such as macrophages and B lymphocytes. This is done in order to prevent T lymphocytes from becoming exhausted or dying off. After then, in order to protect the host from harm that is not unique to the infection, the body downregulates its innate immune response. This is done in order to prevent the host from experiencing injury. When pathogens are eliminated from the body, the innate immune cells, such as macrophages and regulatory DCs, and adaptive regulatory cell types, such as regulatory T cells and B cells, both contribute to the resolution of inflammation. Previous research on the Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and other coronavirus infections, as well as clinical observations in COVID-19 patients, suggest that the course of COVID-19 can be roughly divided into three stages: the first stage (the period up to 7-10 days after the onset of symptoms,0 days to 7-10 days), the second stage (the period from 7-10 to 14-21 days after the onset of symptoms), and the third stage. In the first stage, patients the beginning of the disease's progression (the period from 14-21 days or more after onset of symptoms) In the first stage, the patient is infected with the virus but either does not develop any symptoms or gets flu-like symptoms that range in severity from mild to severe. These symptoms include fever, a dry cough, and exhaustion. In the second stage, the patient develops full-blown symptoms of the illness. During this early stage of the infection, the virus may be recognised by testing known as polymerase chain reaction (PCR), and some people who are infected but do not display symptoms are still able to transmit it on to others. If the immune functions of the patients are robust enough, the virus could be able to be confined, and the patients might then be able to begin the recovery phase of the process. On the other side, let us assume that the patient suffers from immunological dysfunction as a result of their age, gender, comorbidities, or any other ailment that has not yet been recognised.

**Process of the immune system in the human body"**

The human body is home to the immune system, which is responsible for protecting the body from many infections and illnesses (see Figure 1). It is of the utmost significance for both the maintenance of good health and the investigation of the causes of illness. In addition to this, it protects the body against harmful substances, pathogenic agents, and shifts in the condition of the cells (neoplasm) White blood cells are the most essential component of the immune

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system. Because of the intricate network of blood arteries, these cells are able to easily circulate throughout the body, making them a crucial defence mechanism. In order to facilitate monitoring for the presence of foreign germs, the body will allow the lymphatic system to function and will engage in the interchange of cells and fluids between the blood vessels and the lymphatic vessels. The lymphatic vessels are responsible for the transportation of lymph. Each lymph node contains its own distinct compartments, which act as sites where antigens can come into contact with the body. Through the lymphatic veins that are entering the lymph nodes, immune cells and particles from the outer environment make their way to the lymph nodes. As soon as they enter the circulatory system, they are distributed to the many tissues that may be found in different parts of the body. They start the process all over again by looking for foreign antigens in every feasible site, and then they gradually find their way back into the lymphatic system. The lymph nodes and the various compartments of the spleen are locations where immune cells gather, begin their antigen-fighting activities, and carry out their roles in the body.

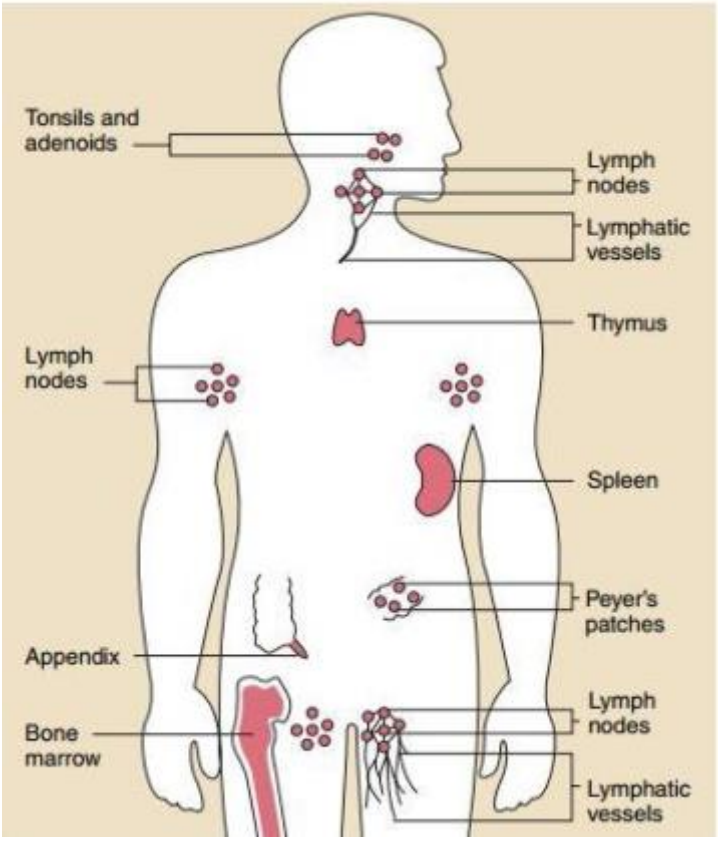


**Fig. 1. The organs of the immune system are positioned throughout the body.**

**Research methodology**

Secondary sources: data collection from journals, books, papers, newspapers, magazines and other sources viz, internet websites .etc.

As we will see in the subsequent discussion, hypothesis-driven systems medicine approaches have a very good chance of rapidly identifying the steps in the interactions between the virus

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and the immune system of the host that are the most important and variable. This is something that can be accomplished relatively quickly. This will make it possible to more accurately stratify patients, which will, in turn, encourage the development of other therapeutic approaches (Rajewsky et al., 2020).

**The breach—point of entry for SARS-CoV-2**

The cell tropism of the virus and its ability to avoid the innate immune responses of the host are two of the most critical elements that define how the host's immune system will react to the infection. Cell tropism refers to the way a virus targets a certain kind of cell. It was immediately apparent, upon the discovery of SARS-CoV-2 and based on its close relationship with the SARS coronavirus (SARS-CoV) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020), that the angiotensin-converting enzyme 2 (ACE2), which is the surface receptor for SARS-CoV, was also a major cellular entry point for SARS-CoV-2. This was discovered after SARS This was a discovery that came as a surprise (Hoffmann et al., 2020). To stimulate its S protein in a manner that is comparable to that of SARS-CoV, SARS-CoV-2 employs the cellular serine protease known as TMPRSS2, which functions in a manner that is akin to that of SARS-CoV. Recent studies have indicated that Neuropilin1 (NRP1) is a crucial cofactor for entry, particularly in cells that exhibit low amounts of ACE2. It has been hypothesised that a variety of other proteases, in addition to furin, participate in the reaction as co-factors.

The Human Cell Atlas (HCA) Lung Biological Network investigated the prevalence of ACE2 and TMPRSS2 in the body by analysing their expression in single-cell RNA sequencing data (scRNA-seq) from multiple tissues from healthy human donors. This allowed the researchers to determine the extent to which these two genes are present throughout the body. Because there were no cell-type-specific expression maps of SARS-CoV-2 viral entry-associated genes, this was carried out (Sungnak et al., 2020). The high co-expression of ACE2 and TMPRSS2 in nasal epithelial cells, in particular in two types of goblet cells and a subset of ciliated cells, showing the highest expression among all cells in the respiratory tree, is probably the factor that is most important for the high efficacy of SARS-CoV-2 transmission. This is because these cells show the highest expression among all cells in the respiratory tree. This expression may be found in the cells that line the nasal passages (Figure 2 A). An intriguing discovery from this research was that these epithelial cells showed a significant "co-expression of genes that are involved in the initial stages of the immune response to viral infections. This discovery showed that specialised nasal cells might potentially play an essential role in both the initial viral infection and the propagation of the virus, as well as potentially playing a part in the viral clearance. In the lung, expression of ACE2 and TMPRSS2 has been mostly seen in alveolar epithelial type II cells. TMPRSS2 is expressed in a wider variety of tissues than ACE2, and cells displaying simultaneous expression have been found in the respiratory tree, the cornea, the oesophagus, the ileum, the colon, the gallbladder, and the common bile duct. However, there is no evidence that immune cells display simultaneous expression. ACE2 is expressed in a wider variety of tissues than

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TMPRSS2. When these findings were extended to even bigger datasets, which included hundreds of unique scRNA-seq datasets created from diverse organisations all over the world, the potential of metadata analysis based on scRNA-seq was identified. In this investigation, it was also possible to forecast the effect of clinical risk factors on the level of gene expression of genes connected with viral entry". These predictions were made possible by the findings of the previous section. In addition to other things, the history of smoking, your age, and your gender are all risk factors. According to the findings of a second study that was carried out by the HCA Lung Biological Network, ACE2 and TMPRSS2 were discovered to be co-expressed in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes. All of these cell types absorb nutrients from the ileum. The findings of the previous study were expanded upon in this study by looking at tissues taken from mice and non-human primates. In contrast to prior research that revealed ACE2 to be an interferon-stimulated gene (ISG), more recent data demonstrated that a shortened version of ACE2 termed deltaACE2, and not ACE2 itself, is an ISG. This form of ACE2 is referred to as deltaACE2. This is due to the fact that deltaACE2 does not serve as a carboxypeptidase and does not bind to the SARS-CoV-2 spike protein.

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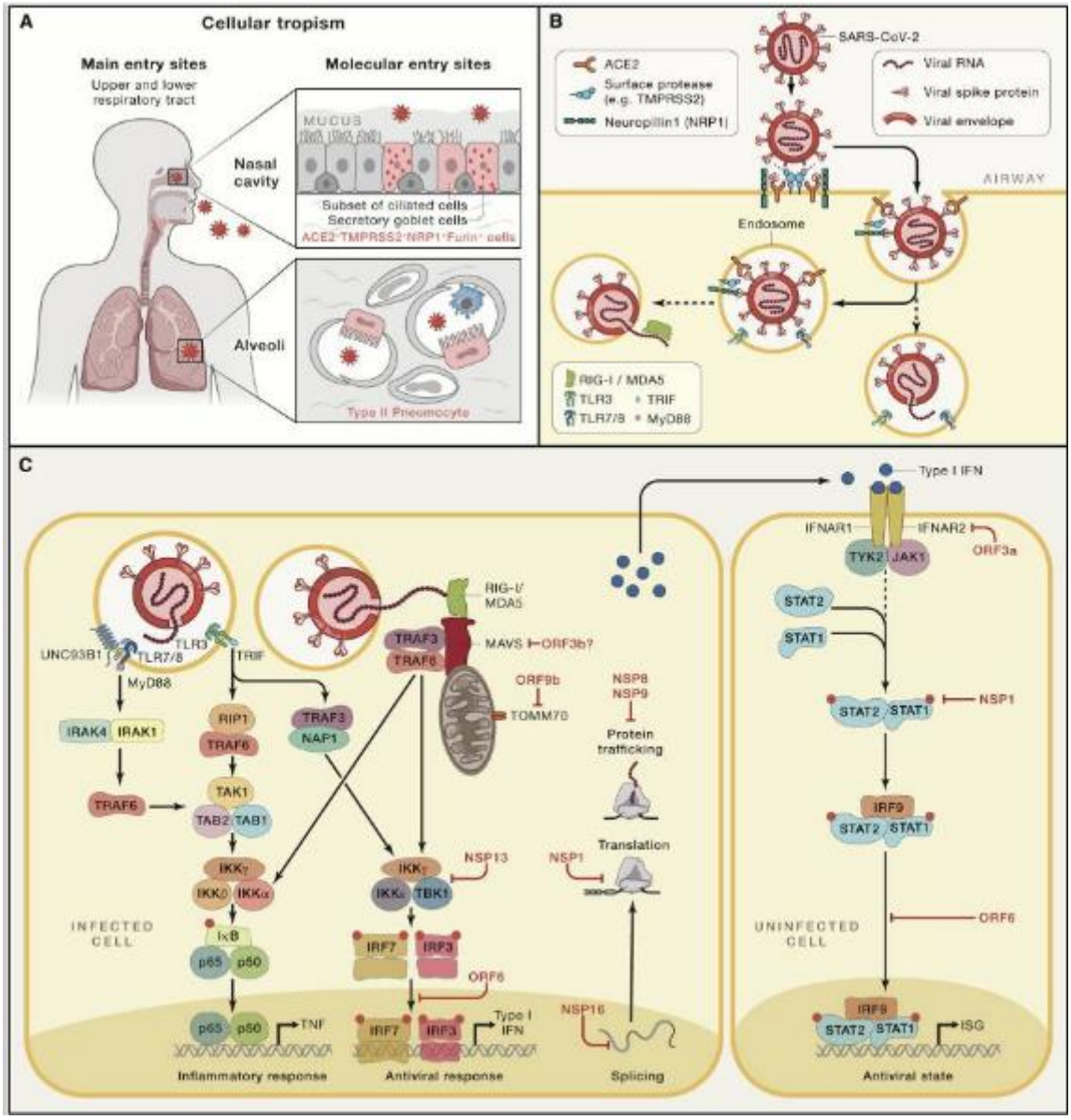


**Figure 2 SARS-CoV-2 tropism, infection, and alarming the innate immune system"**

(A) The major routes of entry for SARS-CoV-2 are the cells that are found within the nasal cavity as well as the upper and lower respiratory tracts.

(B) The molecular factors at play during an infection of a cell by SARS-CoV-2

(C) It is quite likely that the SARS-CoV-2 virus is identified by PRRs that recognise foreign RNA, such as endosomal TLR3 and TLR7, in addition to cytoplasmic RIG-I and MDA5. This is because these PRRs are located in the endosomes. Events farther downstream in the signalling cascade that are predicted to occur as a result of the findings of genetic research, functional and clinical observations, interaction mapping, or CRISPR screening. Connections between viral proteins retrieved from SARS-CoV-2 and cellular processes; or, in the case of information received by interaction mapping, the finding of direct interactions between viral and host proteins. ORF3b was shown to be functionally capable of lowering type I IFN;

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however, a direct target was not discovered (Konno et al., 2020). IRF3/7/9, which stands for interferon regulatory factor 3/7/9; ISG, which stands for interferon-stimulated genes; MDA5, which stands for melanoma differentiation-associated protein 5; RIG-I-like receptor dsRNA helicase enzyme; MyD88, which stands for myeloid differentiation primary response 88; ACE2, which stands for angiotensin-converting enzyme 2; IFNAR1, which stands for interferon-alpha

**Cytokine alterations and innate immune cell responses following infection**

**Alarming the immune system—recognition, interferon response, and immune evasion**

A consistent pattern of cell entrance by endocytosis following receptor engagement has been discovered for coronaviruses. This process occurs after viral RNA is released into the cytoplasm, synthesis of viral proteins, and creation of viral replication/transcription complexes on double-membrane vesicles". After receptor engagement, the next step in this sequence is endocytosis, which allows the molecule to enter the cell. In spite of the extensive study that has been done on the mechanisms that allow SARS-CoV-2 to enter cells, the succeeding phases of the virus's life cycle have not been well investigated. In a similar vein, the pattern recognition receptors (PRRs) that are necessary to the process of detecting SARS-CoV-2 have not yet been properly characterised. This is despite the fact that they are critical to the identification process. According to studies conducted on other coronaviruses, the most plausible possibilities are the Toll-like receptors 3 (TLR3) and TLR7 in the endosome or the cytosolic sensors retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5). These genes are in charge of identifying the RNA of any foreign viruses that may be present (Figure 2B).

**The next phase—from "cytokine storm" to immunosuppression**

It's possible that soluble chemicals including cytokines, chemokines, growth factors, inhibitory factors, hormones, and metabolites might have a local and/or systemic influence on innate immune cells. This is only a notion, though. The transmission and receipt of soluble mediators are both handled by the immune cells that are present at birth. Important disease course-shaping mediators are soluble factors. These factors trigger the release of innate immune cells from the bone marrow into circulation, as well as their recruitment to inflamed and infected tissues, and they also influence the local motility and function of the recruited immune cells. The following are some of the ways in which soluble substances might cause the release of innate immune cells: In COVID-19, cellular responses and interactions are driven by the combination of these parameters, in addition to the time (kinetics), and the concentrations (dynamics) of those factors. These factors are considered to be the "factors of interest (Figure 3).

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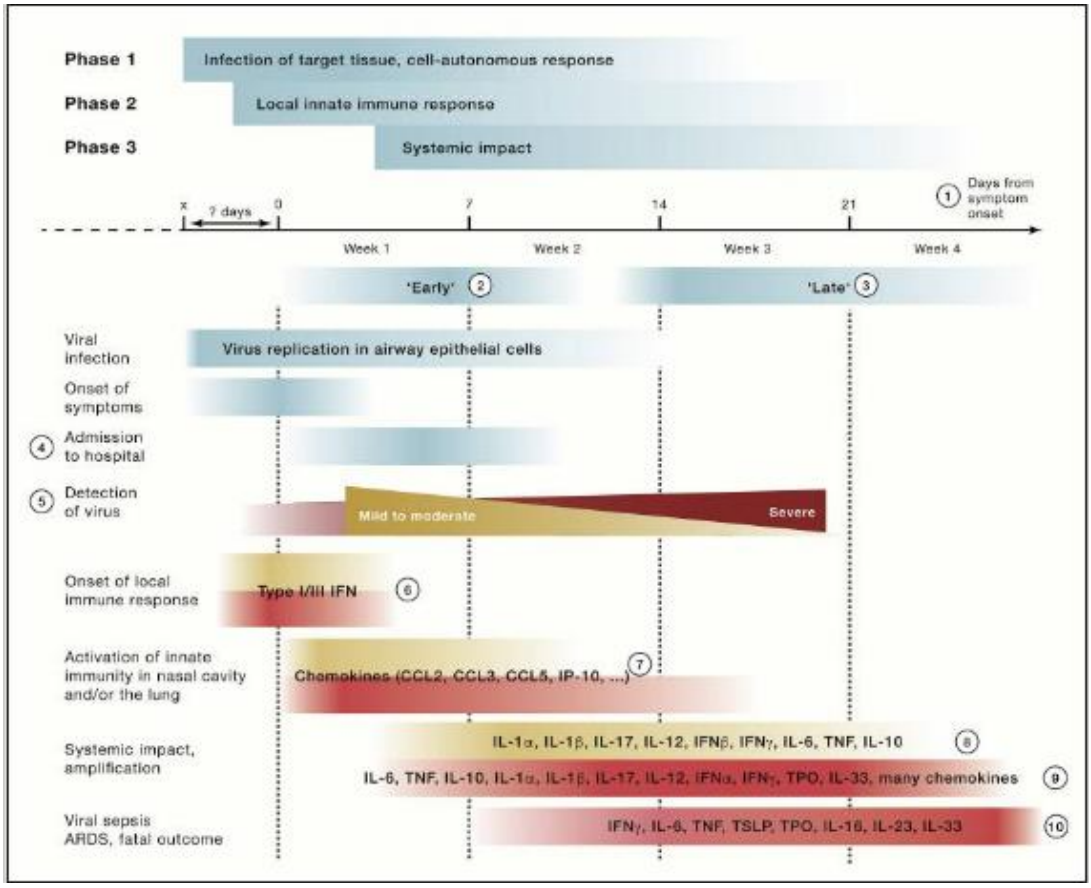


**Figure 3 Soluble mediators during the disease course of COVID-19**

In this piece, we will examine the principles that have been established as a result of the numerous observational studies that have been carried out on the role that soluble mediators play in the innate immune system. These studies have been undertaken on a variety of different topics. The colour red represents the progression of severe illnesses (including critical and fatal ones), whereas the colour yellow represents the progression of mild to moderate sickness. (1) In the context of assessing the kinetics of an illness, the notion of "days from the commencement of symptoms" is becoming an increasingly frequent phrase to use. In the same way that there is a spectrum of possible meanings for this term, there is also a spectrum of possible elapsed timeframes between infection and the development of the first symptoms, as can be seen by the slow fading of colour in the graph. Both of these things should be considered in tandem. These two aspects are equally important and must both be taken into account. (2 and 3) The temporal phases of COVID-19 have not been characterised in the same way in each of the experiments. This is true for each of these points. On the other hand, the majority of studies define "early" as the period of time about 11–25 days after the onset of symptoms, and "late" as the time period up to 10 days after the commencement of symptoms. (4) Being admitted to the hospital was the first data point that was used because of the physical nature of the information it provided. However, the amount of time that passes between a viral infection and admission to the hospital might vary quite a bit. Because of this, it is difficult to compare the results of longitudinal studies that use hospitalisation as the point

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of departure because of the variability in the amount of time that passes between the two events.

## Factors that influence disease severity

### Genetic factors impacting the immune response to SARS-CoV-2

On the basis of the clinical observation that fatal cases included young people who were otherwise healthy, it was hypothesised that host genetics may have a role in the susceptibility of the sickness as well as the severity of it. Multiple international consortia (COVID-19 host genetics project [COVID-19 Host Genetics Initiative, 2020] or the COVID Human Genetic Effort address genetic vulnerability either by conducting genome-wide association studies (GWASs) or by sequencing the whole genome. COVID-19 host genetics project [COVID-19 Host Genetics Initiative, 2020] and the COVID Human Genetic Effort are both examples (WGS). It was hypothesised that signalling pathways that were significant in determining susceptibility to other viral infections may also be significant in determining susceptibility to the COVID-19 virus. Patients with COVID-19 who experienced respiratory failure were discovered to have a gene cluster on chromosome 3 that was a genetic susceptibility locus during an early genome-wide association study (GWAS) that was carried out in Spain and Italy. The results of the COVID-19 Host Genetics Initiative (COVID-19 Host Genetics Initiative, 2020) and the Genetics of Mortality in Critical Care (GenOMICC) GWAS both confirmed the findings of these investigations since they arrived to the same conclusions. Within the COVID-19 risk locus, which is situated on chromosome, immune genes such as CCR9, CXCR6, XCR1, CCR1, and CCR2 are included. The study of comparative genomics has provided conclusive evidence that the COVID-19 risk locus is inherited from Neanderthals and is carried by almost half of the people in South Asia and approximately sixteen percent of the people in Europe.

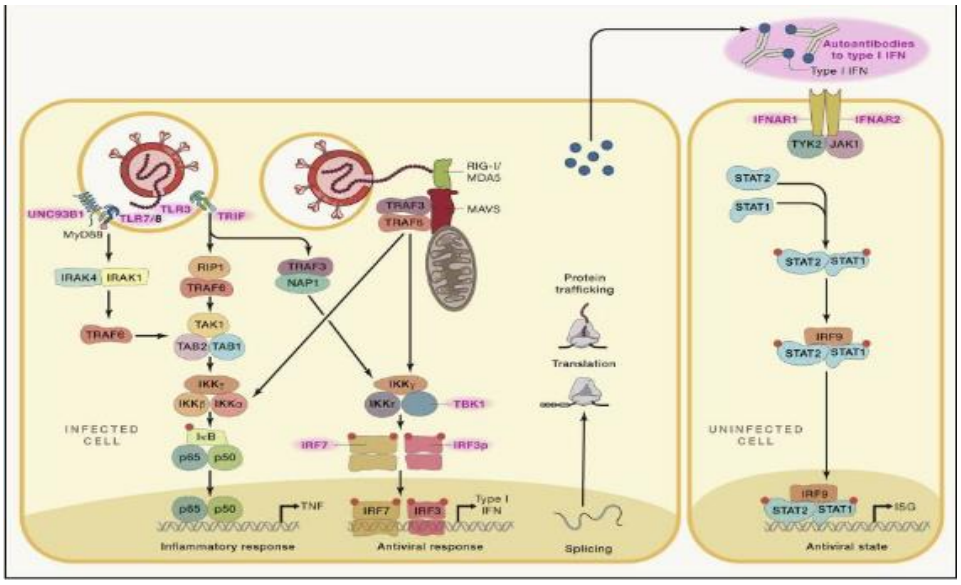


**Figure 4 Genetic factors for COVID-19 susceptibility support the central role of the innate immune system**

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In the highlighted investigations, loss-of-function mutations have already been found in molecules that are involved in the identification of SARS-CoV-2, in addition to critical downstream signalling molecules that are required for a well-orchestrated and robust type I IFN response. These mutations have been found in molecules that are involved in the identification of SARS-CoV-2. The genes that have been determined to have mutations that have caused them to lose their function are represented in a bright pink colour with a pink circle next to them. This is also a good place to view a portrayal of the autoimmune phenocopy of inborn type I IFN immunodeficiency. A list of abbreviations may be found in the caption for Figure 2, which can be found below the figure. Another method was able to identify "variants of the X-chromosomal TLR7 as genetic susceptibility factors by performing genetic variance segregation analysis in two families with young family members (35 years) admitted to the intensive care unit (ICU) due to severe COVID-19". These families both had family members admitted to the ICU due to severe COVID-19 (van der Made et al., 2020). It was discovered that these variations were related with a higher chance of developing COVID-19 (Figure 5). When PBMCs were stimulated with the TLR7 ligand imiquimod, the TLR7 mutations in both families caused a downregulation of downstream genes including IRF7, IFNB1, and ISG15. This was seen following stimulation of PBMCs with imiquimod. Following the stimulation of PBMCs, this was observed as a result. This directly led to a decrease in the amount of IFN- that was produced, hence the problem was solved. When all of these findings are considered together, they suggest that responses including TLR3, TLR7, type I and type II IFNs are necessary components of the immune system in order to regulate SARS-CoV-2 infection. Studies are currently being carried out to determine whether or not the evaluation of these variants can be incorporated in future risk scores that will be used to identify individuals at an elevated risk of developing severe COVID-19 or used in clinical tests that will be used to stratify patients for preventive and novel mechanism-based therapeutic measures. These scores and tests will be used to identify individuals at an elevated risk of developing severe COVID-19.

## Conclusions

In conclusion, patients who survive moderate COVID-19 and severe COVID-19 display a normal immune response that develops from a normal or hypofunctional condition into an enhanced immune response, and then is eventually recovered to the level it was at before the infection. The immunological response in individuals who have fatal COVID-19 can range from reduced function to overactivation, and then finally "to a weaker immune response, which leads to death. It is absolutely necessary, in the current therapy for severe COVID-19" patients, to get a handle on the rise in the number of fatalities. We strongly advise patients to begin interferon treatment as soon as possible after their diagnosis of the condition. Glucocorticoid treatment and intravenous immunoglobulin G should be delivered in the midst of the illness, when the immune response is at its most active. Patients suffering with severe COVID-19 may see an improvement in their condition if they are treated with the appropriate antibiotics and anticoagulant treatment during the stage in which the immune response is hyperactive. It is necessary to do further study on the cellular immune response in COVID-19

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in order to assist us in understanding the pathophysiology of the disease and guiding the treatment in order to enhance the patient's prognosis.

**References**

[1] Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the Novel Coronavirus From the Ongoing Wuhan Outbreak and Modeling of its Spike Protein for Risk of Human Transmission. *Sci China Life Sci* (2020) 63(3):457–60. doi: 10.1007/s11427-020-1637-5

[2] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A Pneumonia Outbreak Associated With a New Coronavirus of Probable Bat Origin. *Nature* (2020) 579(7798):270–3. doi: 10.1038/s41586-020-2012-7

[3] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A Familial Cluster of Pneumonia Associated With the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster. *Lancet* (2020) 395(10223):514–23. doi: 10.1016/S0140-6736(20)30154-9

[4] Ye Q, Wang B, Mao J, Fu J, Shang S, Shu Q, et al. Epidemiological Analysis of COVID-19 and Practical Experience From China. *J Med Virol* (2020) 92(7):755–69. doi: 10.1002/jmv.25813

[5] Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schunemann HJ, et al. Physical Distancing, Face Masks, and Eye Protection to Prevent Person-to-Person Transmission of SARS-CoV-2 and COVID-19: A Systematic Review and Meta-Analysis. *Lancet* (2020) 395(10242):1973–87. doi: 10.1016/S0140-6736(20)31142-9

[6] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical Features of Patients Infected With 2019 Novel Coronavirus in Wuhan, China. *Lancet* (2020) 395(10223):497–506. doi: 10.1016/S0140-6736(20)30183-5

[7] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary Manifestations of COVID-19. *Nat Med* (2020) 26(7):1017–32. doi: 10.1038/s41591-020-0968-3

[8] Berlin D.A., Gulick R.M., Martinez F.J. Severe Covid-19. *N. Engl. J. Med.* 2020;383:2451–2460.

[9] Bernardes J.P., Mishra N., Tran F., Bahmer T., Best L., Blase J.I., Bordoni D., Franzenburg J., Geisen U., Josephs-Spaulding J. Longitudinal Multi-omics Analyses Identify Responses of Megakaryocytes, Erythroid Cells, and Plasmablasts as Hallmarks of Severe COVID-19. *Immunity.* 2020;53:1296–1314.e9.

ISSN- 2394-5125 VOL 07, ISSUE 19, 2020

[10] Blanco-Melo D., Nilsson-Payant B.E., Liu W.-C., Uhl S., Hoagland D., Møller R., Jordan T.X., Oishi K., Panis M., Sachs D. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell.* 2020;181:1036–1045.e9.

[11] Blease K., Mehrad B., Standiford T.J., Lukacs N.W., Kunkel S.L., Chensue S.W., Lu B., Gerard C.J., Hogaboam C.M. Airway remodeling is absent in CCR1-/- mice during chronic fungal allergic airway disease. *J. Immunol.* 2000;165:1564–1572.

[12] Boren E., Gershwin M.E. Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmun. Rev.* 2004;3:401–406.

[13] Bost P., Giladi A., Liu Y., Bendjelal Y., Xu G., David E., Blecher-Gonen R., Cohen M., Medaglia C., Li H. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. *Cell.* 2020;181:1475–1488.e12.

[14] Braun J., Loyal L., Frentsch M., Wendisch D., Georg P., Kurth F., Hippenstiel S., Dingeldey M., Kruse B., Fauchere F. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature.* 2020;587:270–274.