A Seminar Paper on

Immunological Insights into Why Most People Are Asymptomatic With COVID-19 Infection

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Immunological Insights into Why Most People Are Asymptomatic With COVID-19 Infection[1]

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ABSTRACT

COVID-19 is a viral illness caused by the SARS-CoV-2 virus that has rapidly spread worldwide and led to significant morbidity and mortality. One of the notable features of COVID-19 is the high proportion of asymptomatic individuals who are infected with the virus, but do not exhibit any symptoms of illness. Understanding the immunological mechanisms that drive asymptomatic infections is crucial for developing effective disease control measures. This paper provides a comprehensive review of the current knowledge of the immunological aspects of asymptomatic COVID-19 infections. The immune response to COVID-19 varies depending on factors such as age, sex, and comorbidities. Identifying immunological markers that can predict the likelihood of developing asymptomatic COVID-19 infection is an area of active research. Developing effective vaccines that can induce immune responses capable of preventing infection or reducing the severity of symptoms is crucial for controlling the spread of COVID-19. Further research is needed to fully understand the immunological mechanisms of asymptomatic COVID-19 infections and their potential implications for public health.

Keywords: COVID-19, SARS-CoV-2, asymptomatic infection, immune response

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CHAPTER 1

INTRODUCTION

The SARS-CoV-2 virus, which caused the COVID-19 pandemic, has created a global public health crisis resulting in millions of infections and hundreds of thousands of fatalities (Felsenstein *et al.*, 2020). While some people develop severe symptoms, others experience no symptoms or mild symptoms. A distinctive aspect of COVID-19 is that many infected individuals do not exhibit any signs of sickness but can still transmit the virus to other (Johansson *et al.*, 2021). This asymptomatic transmission is a potential obstacle to controlling the pandemic through public health measures (Han *et al.*, 2020). The percentage of asymptomatic COVID-19 cases ranges widely from 6% to 96% (Sattler *et al.*, 2020). To control the virus's spread, it is critical to understand why some people remain asymptomatic while others develop severe symptoms. This variability in clinical presentation has spurred research into the host immune response to the virus.

It is well-established that the host immune response plays a critical role in determining the outcome of viral infections. Studies have shown that the immune response to SARS-CoV-2 is complex, involving both innate and adaptive immunity (Tay *et al.*, 2020). The innate immune response, which is the first line of defense against viral infections, involves the activation of various cells, including macrophages and natural killer cells, and the production of pro-inflammatory cytokines and chemokines. In contrast, the adaptive immune response involves the activation of T and B cells, leading to the production of virus-specific antibodies and the generation of memory cells.

Recent evidence suggests that asymptomatic individuals may mount a more robust innate immune response than symptomatic individuals (Lucas *et al.*, 2020). Similarly, another study found that asymptomatic individuals had higher levels of natural killer cells and cytotoxic T cells than symptomatic individuals (Sekine *et al.*, 2020). These findings suggest that the innate immune response may play an important role in the development of asymptomatic infection.

In addition to the innate immune response, the adaptive immune response may also be involved in the development of asymptomatic infection. Studies have found that asymptomatic individuals have higher levels of antibodies against SARS-CoV-2 than symptomatic individuals (Mahal *et al.*,

2020). Furthermore, asymptomatic individuals may develop a robust T cell response that is capable of targeting and killing infected cells (Weiskopf *et al.*, 2020).

However, the immunological mechanisms that sustain asymptomatic COVID-19 infections are not yet fully understood. The difficulty in detecting asymptomatic infections makes it challenging for public prevention and control of this epidemic (Gao *et al.*, 2021). Factors such as age, sex, and comorbidities are known to impact the vulnerable response to the virus and may determine whether an individual develops symptoms or remains asymptomatic (Sattler *et al.*, 2020). Identifying immunological markers that can predict the likelihood of developing asymptomatic COVID-19 infection is an area of active investigation, as it could provide insight into the underlying mechanisms of the vulnerable response to the virus (Ni *et al.*, 2020).

Based on the above facts the objectives of this reviewed paper are

1. To assess the current understanding of COVID-19 immunology and the immune responses involved in asymptomatic infections.
2. To explore the factors that contribute to the development of asymptomatic COVID-19 infections, such as age, sex, vitamin D and genetic factors.

CHAPTER 2

MATERIALS AND METHODES

Scientific approach requires a close understanding of the subject matter. This paper mainly depends on the secondary data. Different published reports of different journals mainly supported in providing data in this paper. This seminar paper is exclusively a review paper, so all the information has been collected from the secondary sources. It is prepared by browsing internet, studying comprehensively various articles published in different journals, reports, publications, proceedings, dissertation available in the internet. All the information collected from the secondary sources have been compiled systematically and chronologically to enrich this paper.

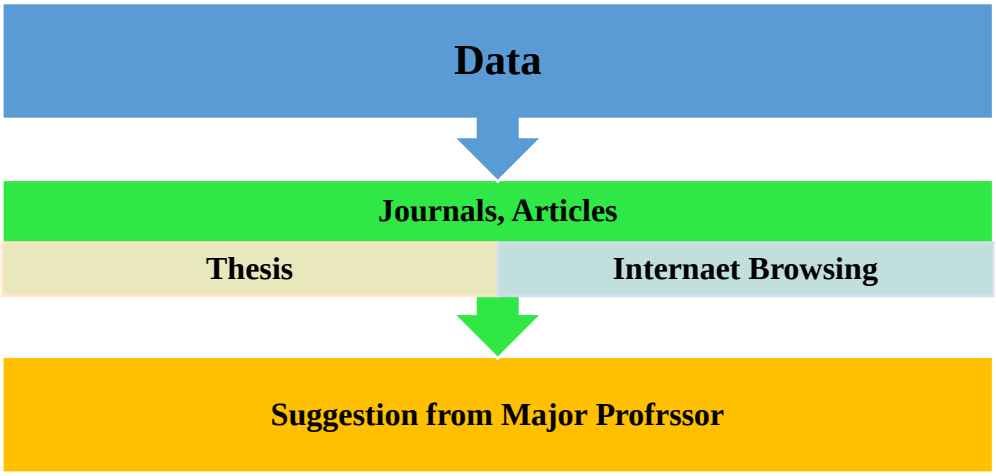


Figure 1. Sources of data and information used in the present paper.

CHAPTER 3

REVIEW OF FINDINGS

3.1 Immunology

Immunology is the study of the immune system and its functions in defending the body against infectious agents and other foreign substances. There are mainly two types of immunity and these are innate immunity and adaptive immunity (Figure 2).

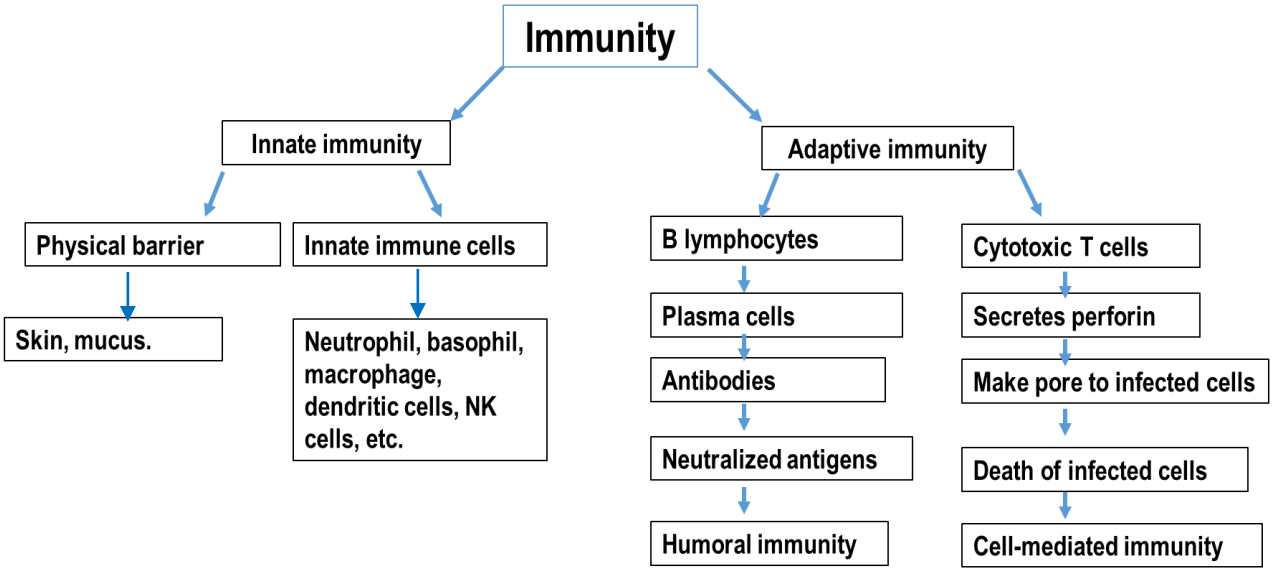
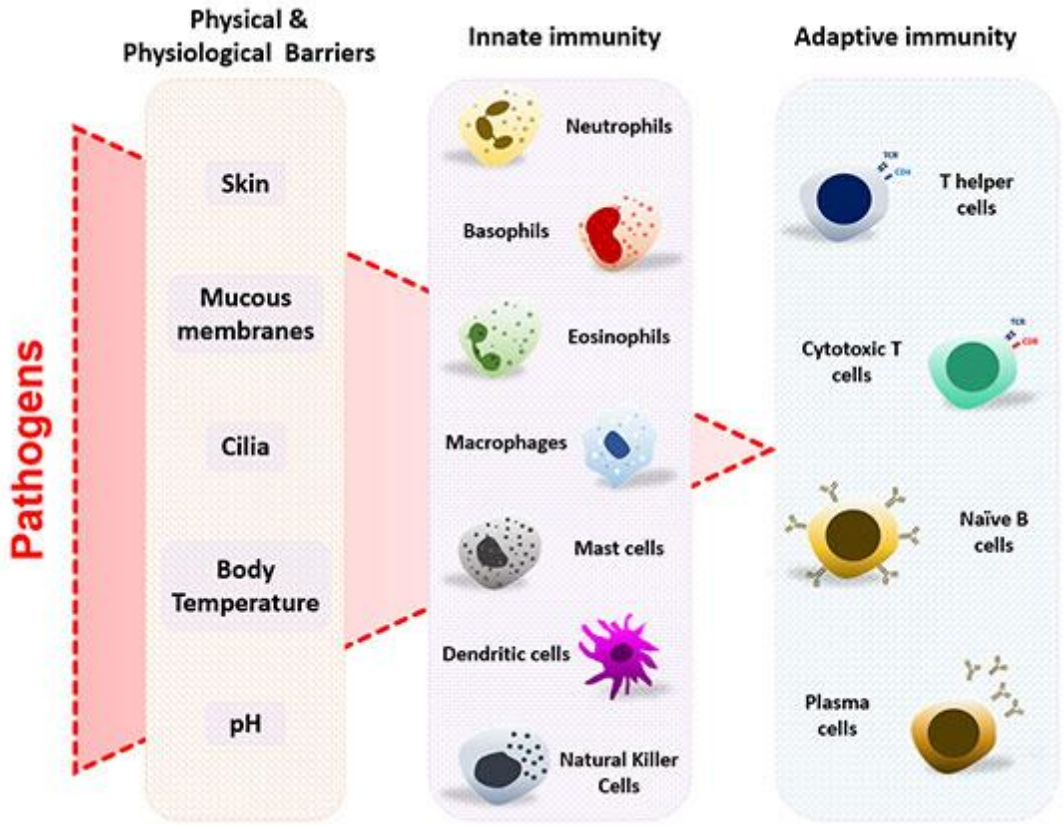


Figure 2. Types and functions of immunity. Source: (Alam , 2023)

The first line of defense against pathogens is physical barriers such as skin and mucous membranes. These structures prevent pathogens from entering the body and can also trap and remove them (Ni *et al.*, 2020). If a pathogen breaches the physical barriers, the next line of defense is innate immune cells. This is a non-specific immune response that includes macrophages, natural killer cells, and neutrophils that phagocyte the pathogens as well as secrete inflammatory mediators that activate adaptive immunity. If the innate immune system is unable to eliminate the pathogen, the third line of defense is adaptive immunity is activated. This is a highly specific immune response. Adaptive immunity includes the production of antibodies by B cells and the activation of cytotoxic T cells, which can directly kill infected cells (Marshall *et al.*, 2018). Once

the pathogen has been eliminated, adaptive immunity also provides long-term protection against future infections by the same pathogen (Figure 3).



Source: (Ba, 2013)

Figure 3. Layers of immune system.

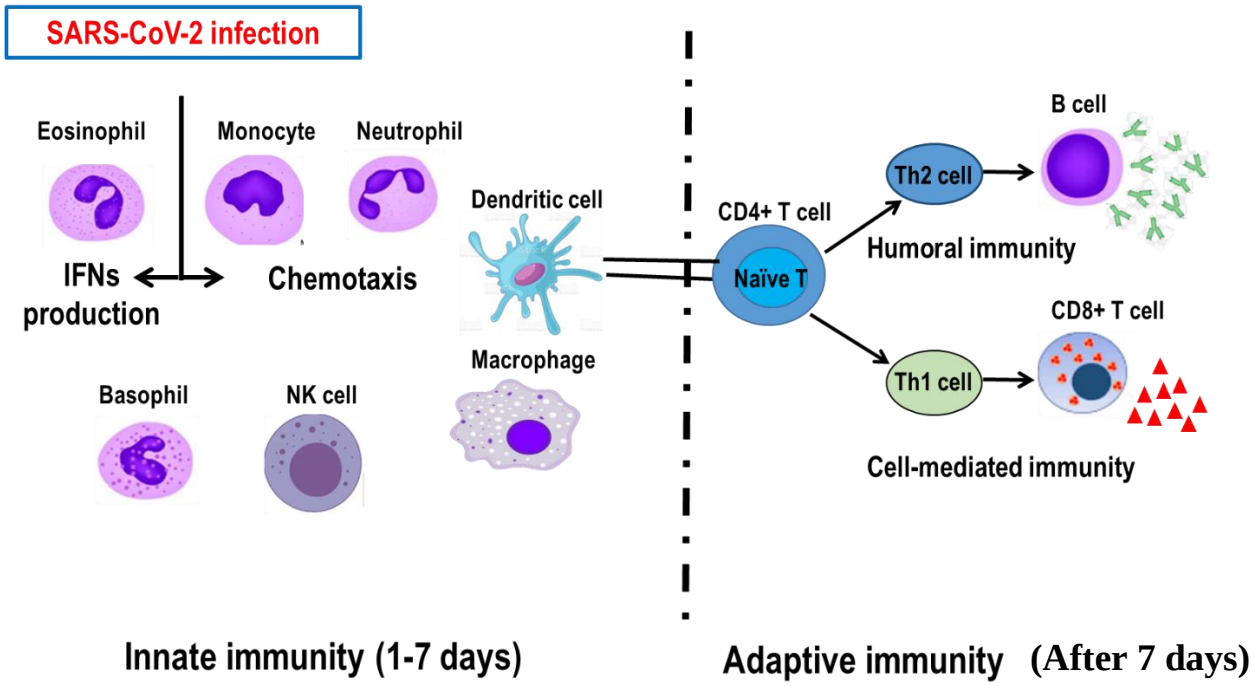
3.2 Adaptive immunity (Humoral and cellular immunity)

The adaptive immunity comprised of humoral immunity and cell-mediated immunity. The humoral immunity involves the production of antibodies by B cells, which neutralizes specific antigens. And the cell-mediated immunity involves the activation of cytotoxic T cells, which can directly kill infected cells by perforin and granzymes which make pore and lyses the infected cell membrane (Ba, 2013).

3.3 General Mechanism of Immune System

Foreign particles enter into the body and release INFs by chemotaxis process. Increase the secretion of phagocytic cell and the phagocytic cells try to engulf the foreign particles. This innate immune activity occurs within (1-7) day of entering the foreign particles. If the innate immune

system fails to phagocyte or prevent the infection then adaptive immune system starts the mechanism to prevent the body. Antigen presenting cells communicate with naïve T cell and then convert into either Th 2 cell and result humoral immunity or Th 1 cell and result cellular immunity after 7 days of entering the foreign particle into the body (Alam & Czajkowsky, 2022).



Source: (Alam & Czajkowsky, 2022)

Figure 4. Mechanism of innate and adaptive immunity.

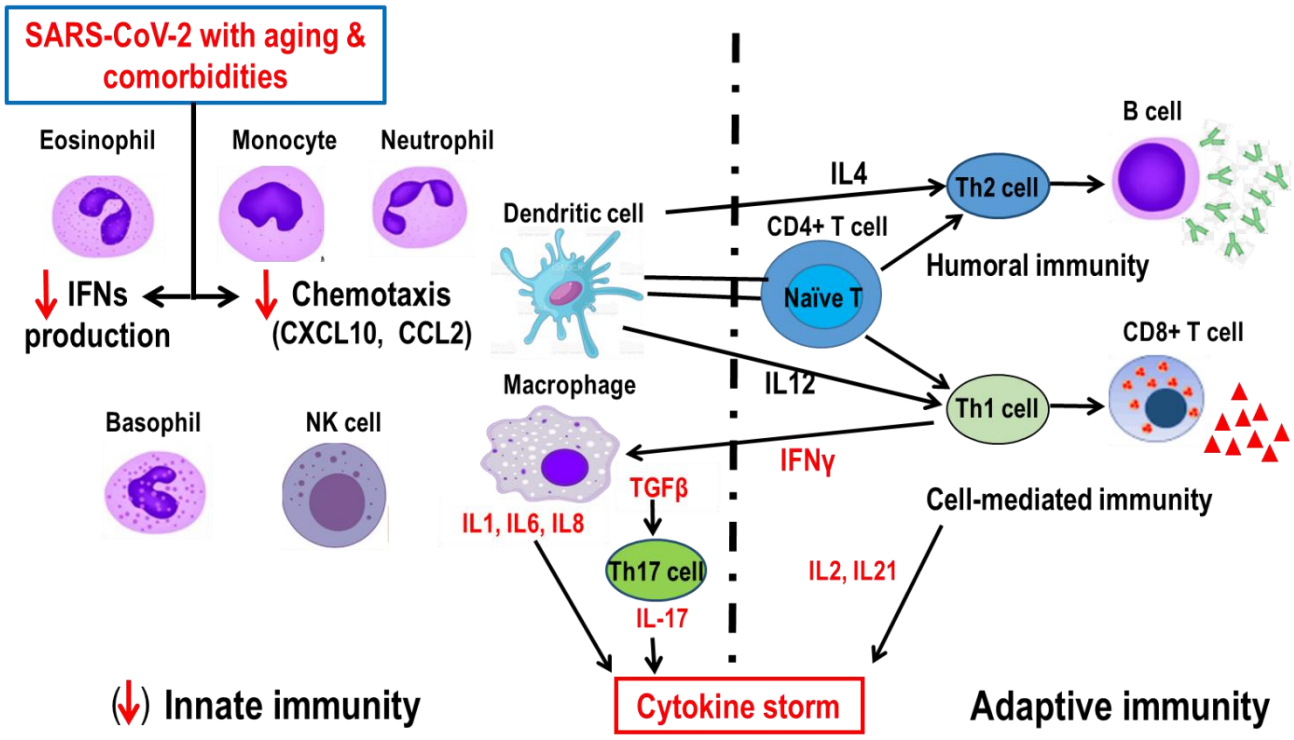
3.4 Immune Mechanism During COVID-19 Infection and cytokine storm

When the SARS-CoV-2 virus that causes COVID-19 infects the body, it is recognized by immune cells such as dendritic cells and macrophages. These cells engulf the virus and present its antigens to other immune cells, including T cells and B cells.

The activation of T cells is thought to play a critical role in the immune response to COVID-19. CD4+ T cells can differentiate into several subsets, including T helper 1 (Th1) cells, which produce cytokines such as interferon-gamma (IFN-γ) that help to activate other immune cells, and T helper 2 (Th2) cells, which are involved in the production of antibodies. CD8+ T cells, also known as cytotoxic T cells, can recognize and kill infected cells that display viral antigens on their surface. This is an important mechanism for controlling viral replication and limiting the spread of the

infection (Chen & John, 2020).B cells also play an important role in the immune response to COVID-19 by producing antibodies that can recognize and bind to the virus. These antibodies can neutralize the virus and prevent it from infecting cells, as well as mark the virus for destruction by other immune cells (Shi *et al.*, 2020).

The immune response to COVID-19 can also lead to the activation of inflammatory pathways, which can cause tissue damage and contribute to the symptoms of the disease. In severe cases of COVID-19, an excessive immune response, known as a cytokine storm (Figure 5), can occur, leading to widespread inflammation and tissue damage.



Source: (Alam & Czajkowsky, 2022)

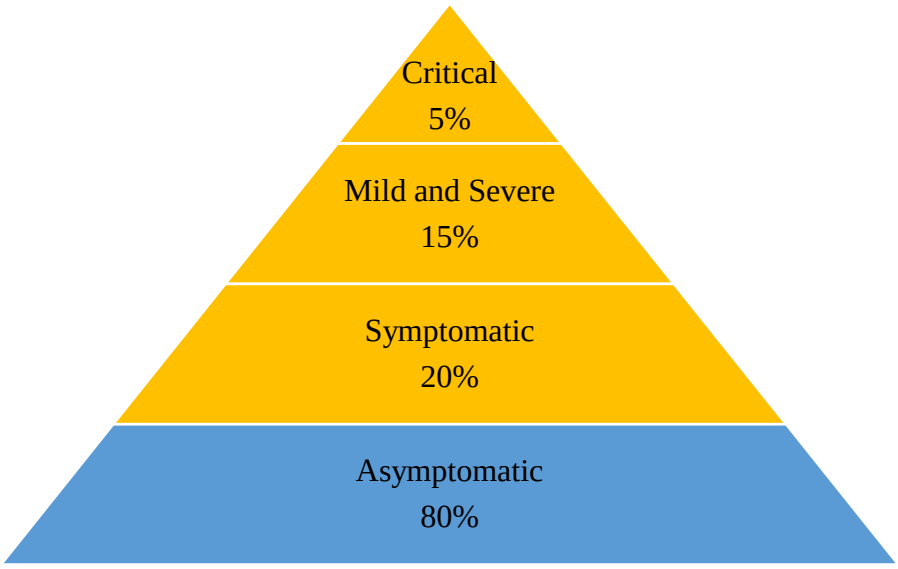
Figure 5. Cytokine storm.

3.5 Asymptomatic COVID-19 Infection

The immune response to COVID-19 infection varies from person to person and depends on various factors, including the severity of the infection, age, and underlying health conditions. Asymptomatic COVID-19 infection refers to cases in which an individual has been infected with the virus but does not show any symptoms of the disease. These case can be challenging to identify

and control, as individuals may unknowingly spread the virus to others (Li *et al.*, 2020). Recent studies have found that asymptomatic cases of COVID-19 are not uncommon, with some estimates suggesting that up to (40-45)% of infected individuals may not experience symptoms (Mizumoto *et al.*, 2020).

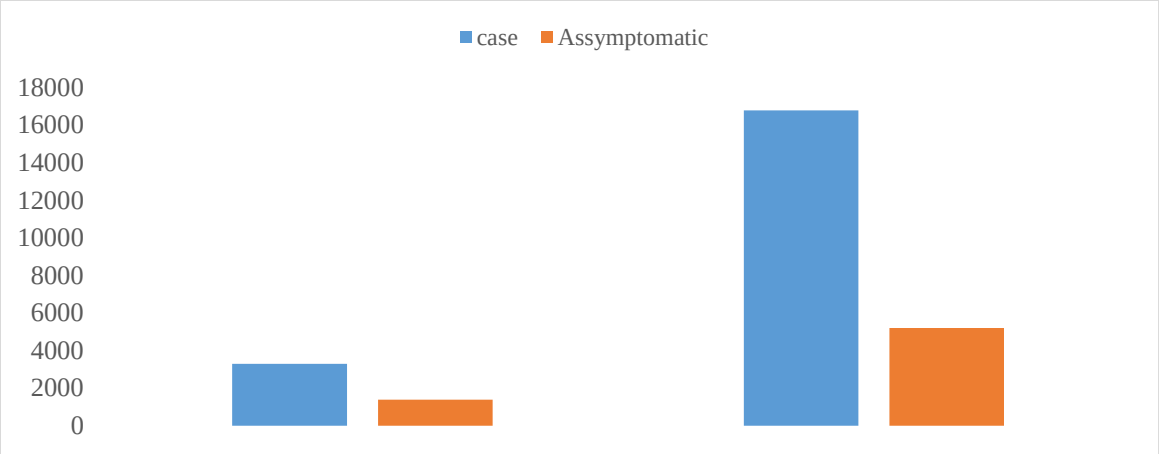
Epidemiological studies suggest that most of the COVID-19 patients, about 80% are asymptomatic, 20% showed symptoms characterized by fever, cough and phenomena, etc. Among 20% of symptomatic cases 15% had mild and severe symptom and 5% were critical. Among critical (1-2)% were dead (Figure 6) (Wu & McGoogan, 2020).



Source: (Wu & McGoogan, 2020)

Figure 6. Different case ratio of COVID 19 infection.

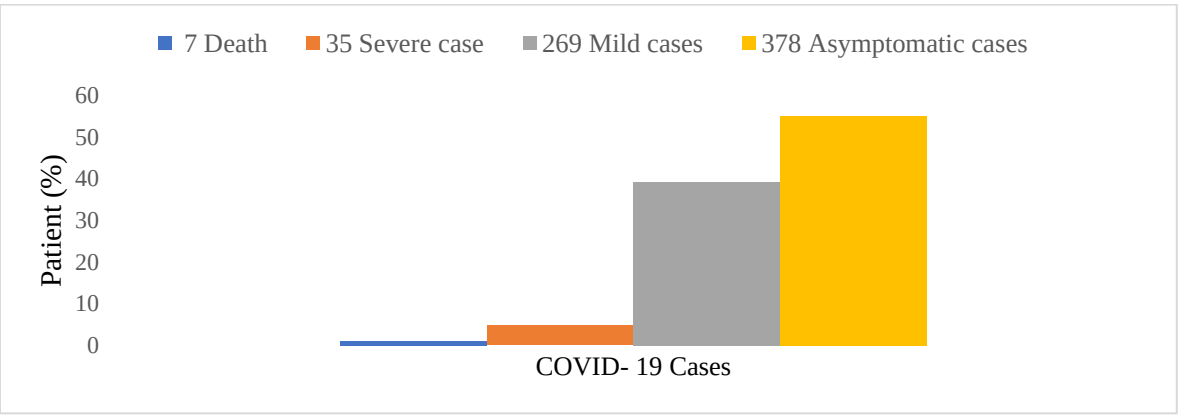
The immunological insight of why most of the people are asymptomatic is not clearly described at all. A study conducted in Italy and published in the journal Nature in August 2020 reported that among 3,300 residents of the municipality of Vo', 42% of SARS-CoV-2 positive individuals were asymptomatic at the time of testing (Figure 7) (Lavezzo *et al.*, 2020). A study conducted in the United States and published in the Annals of Internal Medicine in November 2020 reported that among 16,780 participants who had tested positive for SARS-CoV-2, 69% reported experiencing symptoms at the time of testing, while 31% were asymptomatic (Figure 7) (Oran & Topol, 2020).



Source: (Lavezzo *et al.*, 2020; Oran & Topol, 2020)

Figure 7. COVID-19 cases with asymptomatic percentages.

In the Expert Taskforce for the COVID-19 Cruise Ship Outbreak the proportion of fatal, severe, mild, and asymptomatic COVID-19 cases were recorded among 544 passengers and 143 crew. Among 3,711 people aboard, 687 (18.5%) developed confirmed COVID-19; of these, 378 (55.0%) were asymptomatic (Figure 8) (Assessment & Open, 2020).



Source: (Assessment & Open, 2020)

Figure 8. COVID-19 outbreak in Cruise Ship.

Baggett *et al.*, (2020) studied SARS-COV-2 outbreaks in homeless shelters in Boston, USA and found 87.8% asymptomatic patients with fever, cough, shortness in breath. Another study also found 52.9% asymptomatic patient with same symptoms shown in (Table. 1) (Imbert *et al.*, 2021).

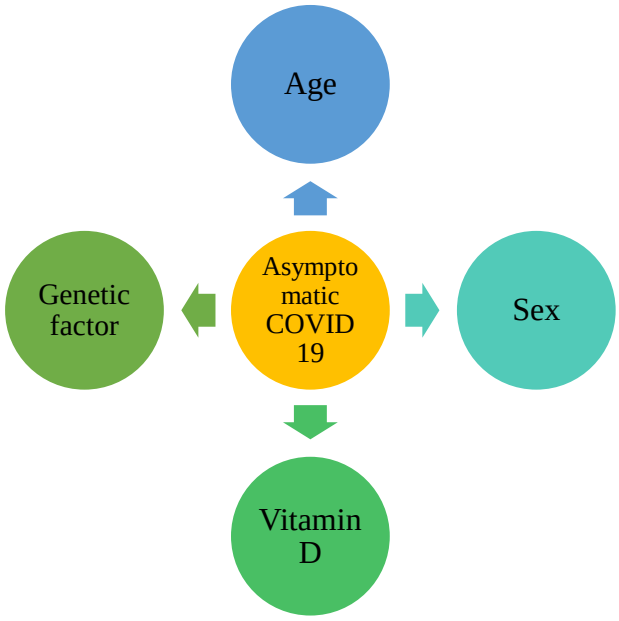
Table 1. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreaks in homeless shelters available in the scientific literature

Location	SARS-CoV-2 Positive (%)	Symptoms	Asymptomatic rate (%)	Author
Boston, USA	36%	Fever (0.7%), cough (7.5%), shortness of breath (1.4%)	87.8%	(Baggett *et al.*, 2020)
Seattle and King County, USA	18.5 %	Not reported	Not reported	(Tobolowsky *et al.*, 2020)
San Francisco, USA	67%	Fever, cough, shortness of breath, pain when breathing	52.9%	(Imbert *et al.*, 2021)

Source: (Imbert *et al.*, 2021).

3.6 Factors involved into asymptomatic COVID-19 Infection

The factors that contribute to asymptomatic COVID-19 infection are not yet fully understood, but several factors have been suggested based on available evidence including the severity of the infection, age, sex, underlying health conditions, etc. (Tay *et al.*, 2020).

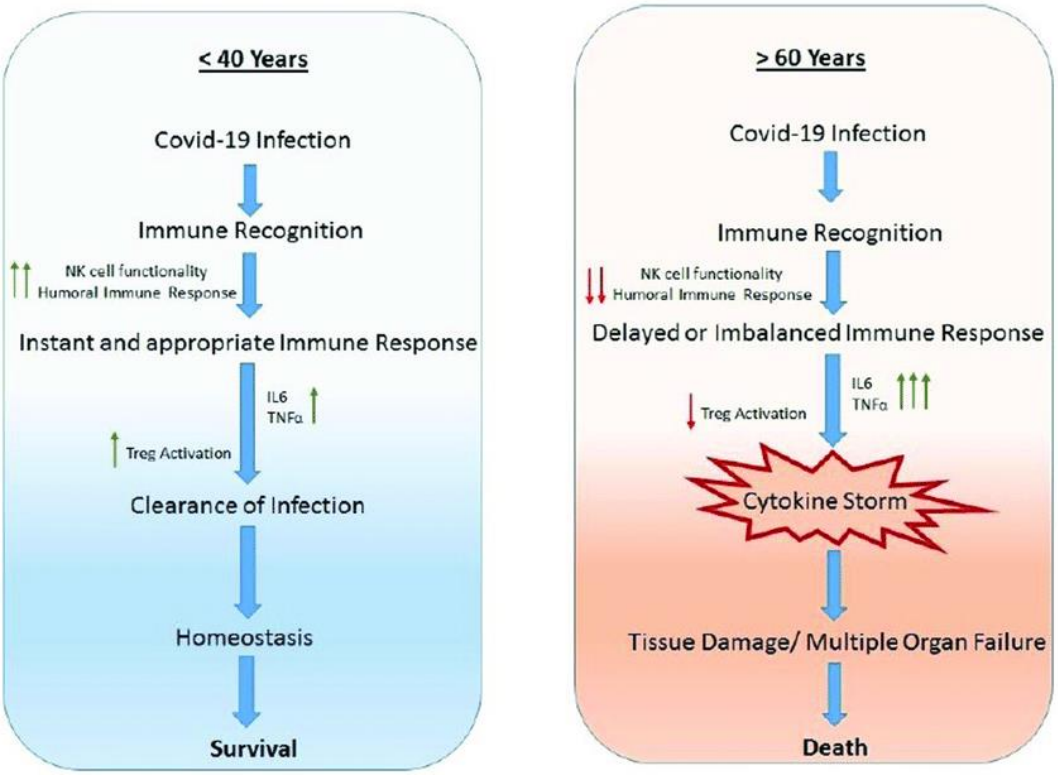


Source: (Tay *et al.*, 2020).

Figure 9. Factors involved in asymptomatic COVID 19 infection most of the people.

3.6.1 Immunological insight into asymptomatic COVID- 19 infection and age

A major factor that contributes to COVID-19 deaths among the elderly is the cytokine storm, which occurs when the immune system overreacts and releases too many pro-inflammatory cytokines. This hyper-inflammatory response is more likely to occur in older individuals with underlying health conditions, as their immune systems are more likely to be imbalanced. The cytokine storm leads to further loss of immune regulation and an excessive immune response to inflammation. As a result, there is an influx of immune cells to the site of inflammation, which can exacerbate the disease (Figure 10) (Sherwani & Khan, 2020).

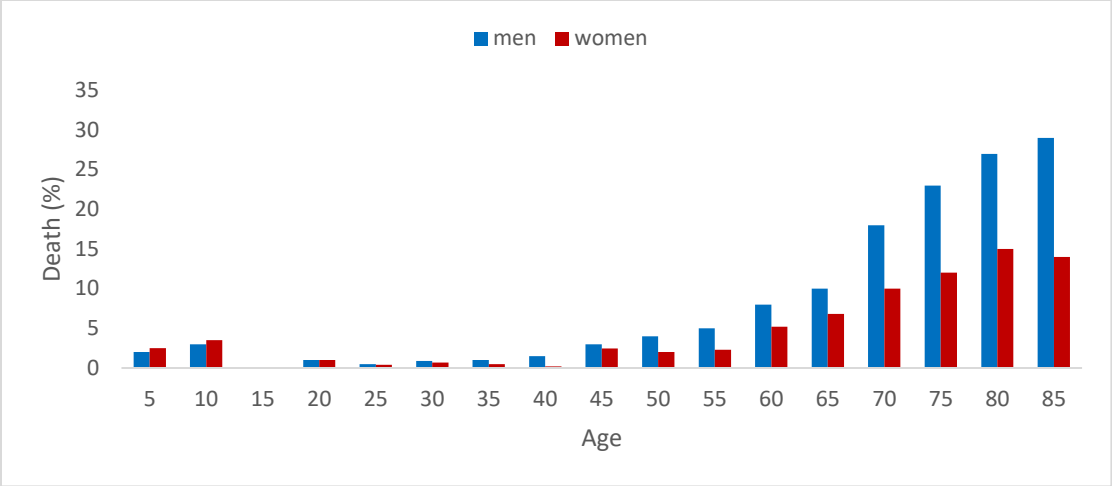


Source: (Sherwani & Khan, 2020)

Figure 10. Comparison of immune responses in Covid-19 infection in individuals 60 years old.

3.6.2 Immunological insight into asymptomatic COVID- 19 infection and sex

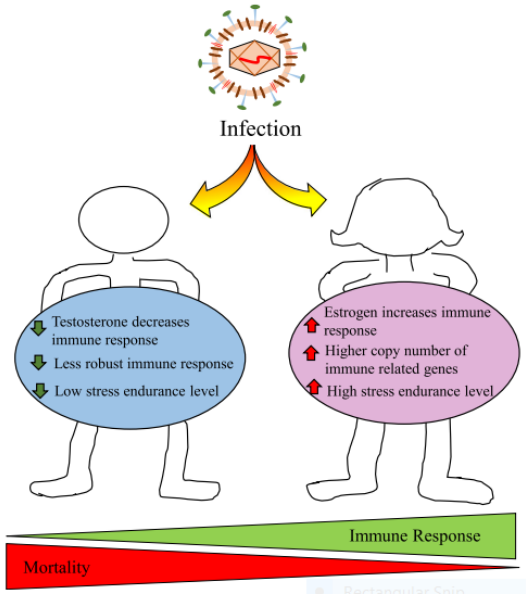
Men have a higher rate of infection with SARS-CoV-2 than women, with 58.1% of cases being male and 41.9% being female. Men were more vulnerable to SARS-CoV-2 infection, with a death rate in some strata that is roughly 50% higher than that in women (Figure 11) (Seeland *et al.*, 2020).



Source: (Sherwani & Khan, 2020)

Figure 11. COVID- 19 death rates in percent for women (red) and men (blue).

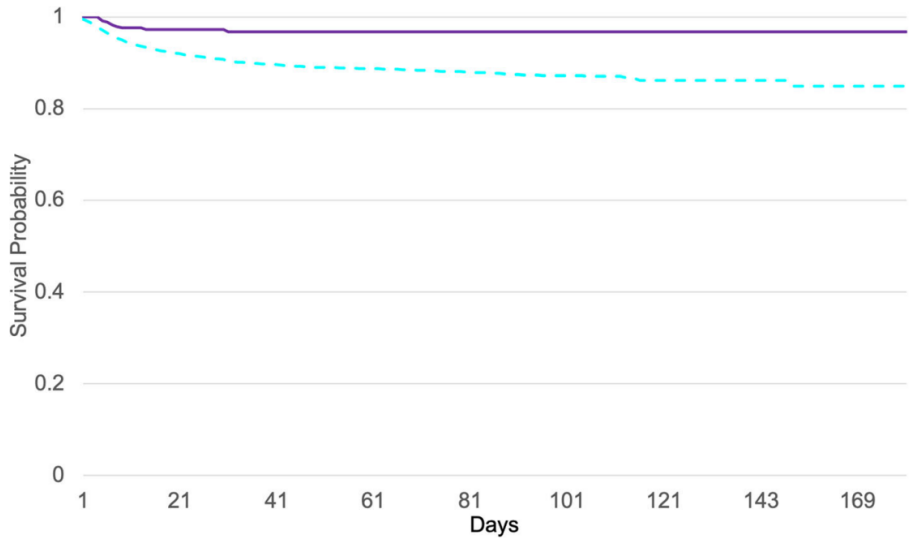
COVID-19 has exhibited a gender-biased pattern of mortality, with a higher fatality rate observed among males. This gender difference may be attributed to the varying effects of testosterone and estrogen on the immune system. Females, having two X chromosomes, possess a greater number of immune-related genes, which confers a more potent immune response. The more robust immune system in females is better able to control viral infections, leading to a lower mortality rate (Figure 12). Another possible explanation for the gender-specific pathogenesis of COVID-19 is that males have a lower level of stress endurance compared to females (Pradhan & Olsson, 2020).



Source: (Pradhan & Olsson, 2020)

Figure 12. The possible factors in sex-biased mortality from COVID-19.

Women may have an advantage in immune cell regulation due to the beneficial effects of estradiol, which can inhibit interleukin 6 (IL6) and stabilize the immune system. IL-6 is a cytokine that can have both anti-inflammatory and pro-inflammatory effects, and it is produced by various stromal and immune system cells such as monocytes, lymphocytes, macrophages, endothelial cells, mast cells, and dendritic cells. It is thought to play a crucial role in triggering cytokine storms, which result in severe symptoms in individuals infected with SARS-CoV-2 (McGonagle *et al.*, 2020). Interestingly, the female hormone 17β-estradiol inhibits the IL-6 cytokine pathway, whereas male hormones (androgens) increase the production of IL-6 (Tevfik & Karpuzoglu, 2012). As a result, woman has more survival rate than man due to estrogen (Figure 13).



Source: (Tevfik & Karpuzoglu, 2012)

Figure 13. The survival probability of women who were estradiol users (violet line) is shown, alongside nonusers (blue dashed line)

3.6.3 Immunological insight into asymptomatic COVID- 19 infection and vitamin D

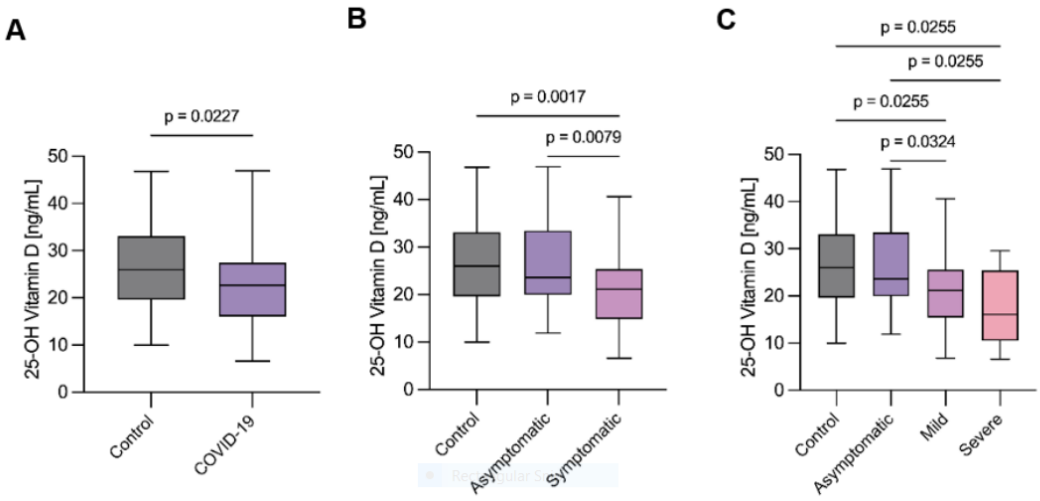
The correlation between vitamin D deficiency and COVID-19 infection has been examined, with some studies suggesting that insufficient levels of vitamin D may increase the risk and severity of COVID-19 (Anderson & Grimes, 2020). A statistically significant difference was found in a study results by vitamin D concentration in terms of deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), and sufficiency (≥30 ng/mL) (Anderson & Grimes, 2020). Twenty (45.4%) pregnant women in the mild COVID-19 group and six (60%) in the severe group were deficient in vitamin D ($p = 0.030$) (Table 2) (Anderson & Grimes, 2020).

Table 2. Distribution of the patients according to 25-OH vitamin D levels

Group	COVID-19 Negative n (%)	Asymptomatic COVID-19 n (%)	Mild COVID-19 n (%)	Severe COVID-19 n (%)	p-Value
Sufficiency ≥ 30 ng/mL	30 (39%)	10 (31%)	6 (14%)	0	
Insufficiency 20–30 ng/mL	29 (37%)	14 (44%)	18 (41%)	4 (40%)	0.015
Deficiency < 20 ng/mL	20 (25%)	8 (25%)	20 (45%)	6 (60%)	

Source: (Anderson & Grimes, 2020)

All pregnant women who tested positive for COVID-19, whether they were asymptomatic or symptomatic, had lower levels of serum 25-OH vitamin D compared to the control group (p = 0.027) (Figure 14A). Among pregnant women with COVID-19, those who had symptoms had significantly lower serum vitamin D levels compared to those who were asymptomatic (p = 0.0079) and healthy pregnant controls (p = 0.0017) (Figure 14B). However, there were no significant differences in vitamin D levels between asymptomatic COVID-19 pregnant women and healthy pregnant controls. Furthermore, patients with severe COVID-19 symptoms had significantly lower vitamin D concentrations than the control group (p = 0.0255) (Figure 14C) (Anderson & Grimes, 2020).

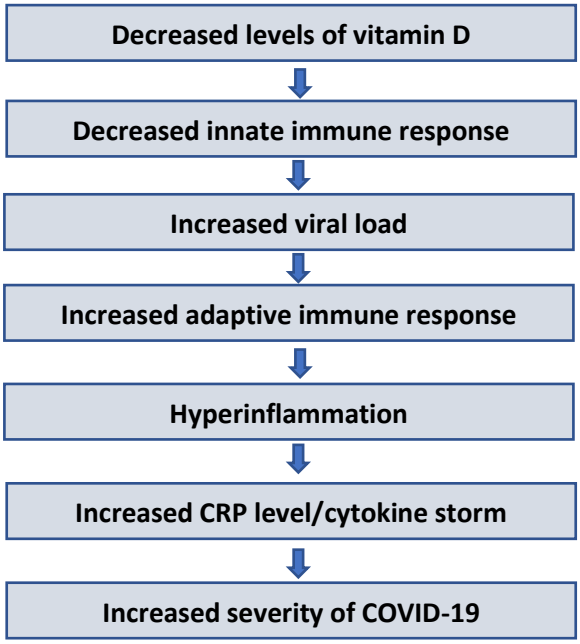


Source: (Anderson & Grimes, 2020)

Figure 14. Serum 25-OH vitamin D levels in COVID-19 and control women in the third trimester of pregnancy. (A) 25-OH vitamin D levels in healthy pregnant women and COVID-19 group. (B)

25-OH vitamin D concentrations between asymptomatic and symptomatic group compared with control. (C) 25-OH vitamin D levels according to symptomatology.

Vitamin D has the ability to decrease the production of cytokines and CRP while simultaneously enhancing the innate immune system. This may result in a reduction of the viral load and a decrease in the excessive activation of the adaptive immune system, which could lead to a reduction in mortality associated with COVID-19 (Alam *et al.*, 2021). Figure 15. shows that decreased level of vitamin D causes the delayed immune response and increased the viral load that ensure the adaptive immune response. As a result, hyperinflammation occurs and finally cytokine storm found and that enhance the infection or severity rate. So, increased level of vitamin D causes the alternative effects. The person who has enough vitamin D or increased vitamin D the produce instant immune response and no cytokine storm and remain as asymptomatic to Covid-19 infection.



Source: (Alam *et al.*, 2021)

Figure 15. Schematic representation of a possible correlation between vitamin D deficiency and COVID-19 severity.

COVID-19 decreases the innate immune response and ACE2 expression but increases the cytokine levels (Table 3).

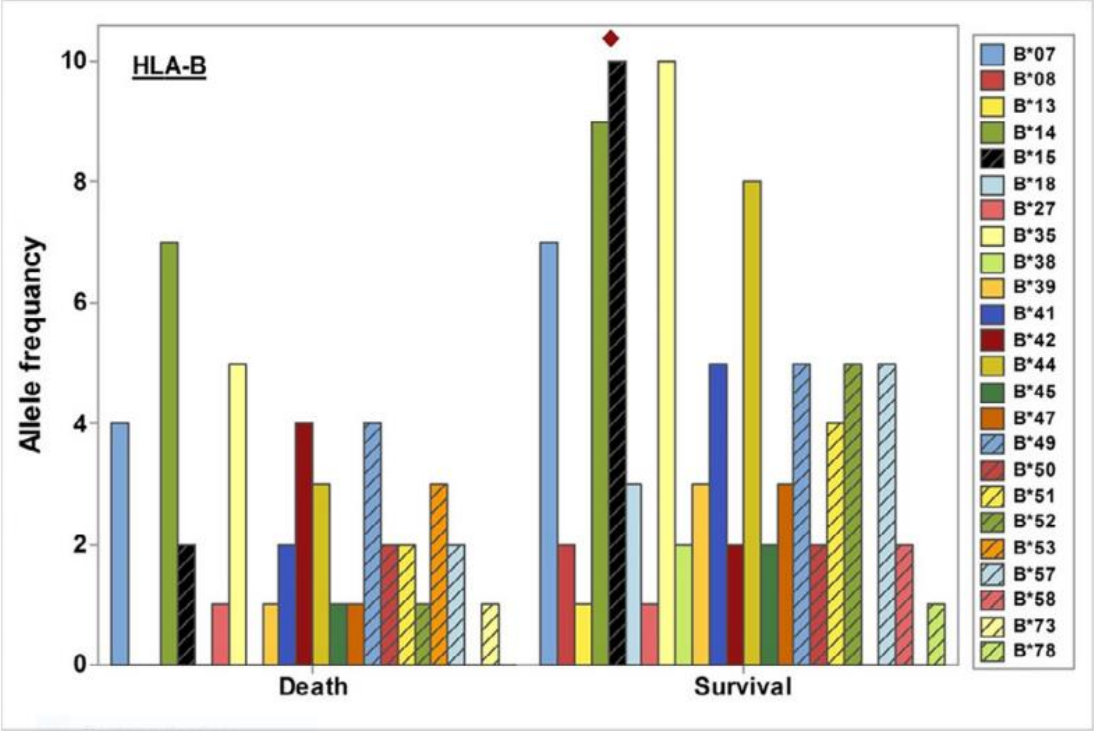
Table 3. Biochemical correlations between COVID-19 and vitamin D deficiency

Parameters	**COVID-19**	**Vitamin D deficiency**
IL-6	Increased	Increased
TNF-α	Increased	Increased
IFNγ	Increased	Increased
C-reactive protein	Increased	Increased
D-dimer	Increased	Increased
Innate immune response	Decreased	Decreased
Th1 adaptive immune response	Increased	Increased
Cytokine storm	Increased	Increased
ACE2 expression	Decreased	Decreased
Coagulability	Increased	Increased

Source: (Alam *et al.*, 2021)

3.6.4 Immunological insight into asymptomatic COVID- 19 infection and genetic factor

HLA-B*15:01 is the particular gene that makes up the MHC-1. It is composed of two gene allele, one gene allele from mother and one gene allele from father. This HLA-B*15:01 is associated with asymptomatic SARS cov2 infection (Augusto *et al.*, 2022). Certain HLA alleles have been found to be associated with severe COVID-19 pneumonia, while the presence of HLA-B*15 has been strongly associated with better survival outcomes (Abdelhafiz *et al.*, 2022). In (Figure 16.) HLA-B*15 was significantly associated with protection against mortality.



Source: (Abdelhafiz *et al.*, 2022

Figure 16. Frequency of HLA-B in correlation with the mortality from the disease frequency of different HLA-B alleles in correlation with the mortality from COVID-19.

After categorizing patients based on their risk factors and the severity of their COVID-19 condition, certain HLA alleles showed a significant correlation with severe COVID-19 pneumonia. Conversely, the presence of HLA-B*15 was strongly associated with survival of the people or produce strong immunity that's why infected people don't show any symptoms and remain asymptomatic.

CHAPTER 4

CONCLUSION

COVID-19 has become a significant public health challenge worldwide, with millions of people infected and hundreds of thousands of deaths. The immunity is dictator of the disease outcome, including COVID-19. Although the immune response to SARS-CoV-2 is complex, most of the people are asymptomatic. The immunological insights of asymptomatic COVID-19 have not been clearly described yet. Recent evidence suggests that asymptomatic individuals may mount a more robust immune response.

Younger people are more asymptomatic than older, male has more infection and death rate than female. People who have optimum level of vitamin D their immune system is stronger than people who has low or insufficient level of vitamin D. Further exploration into immunological markers that can predict the likelihood of developing asymptomatic COVID-19 infection is an area of active research. Understanding the immune response and factors that contribute to the development of asymptomatic infections is critical for developing effective strategies to control the spread of the virus and ultimately mitigating its impact on global public health.

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