Major factors affect the severity of COVID-19: A review

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Abstract

People in different conditions and environments shows different levels of severity of COVID-19. This review states five factors affecting the severity of COVID-19 that can be classified into two categories, innate factors, and external factors, which are backed up by the analysis of statistical data on medical primary research. Five main points were listed, the variation in human genotype-some particular gene section founded by other studies relevant to the severity; Immune responses-how does different groups of people who have different feature affect the severity. Age, comorbidities such as cancer (shown in Fig1, cancer cells) and vaccinated vs unvaccinated people; Clinical factors-how does patients been hospitalized; Variants of SARS-Cov-2, the different in virus characteristics affect the severity; Environmental factor- why people react differently in various environments. In no particular order. In this essay, every points will be discussed.

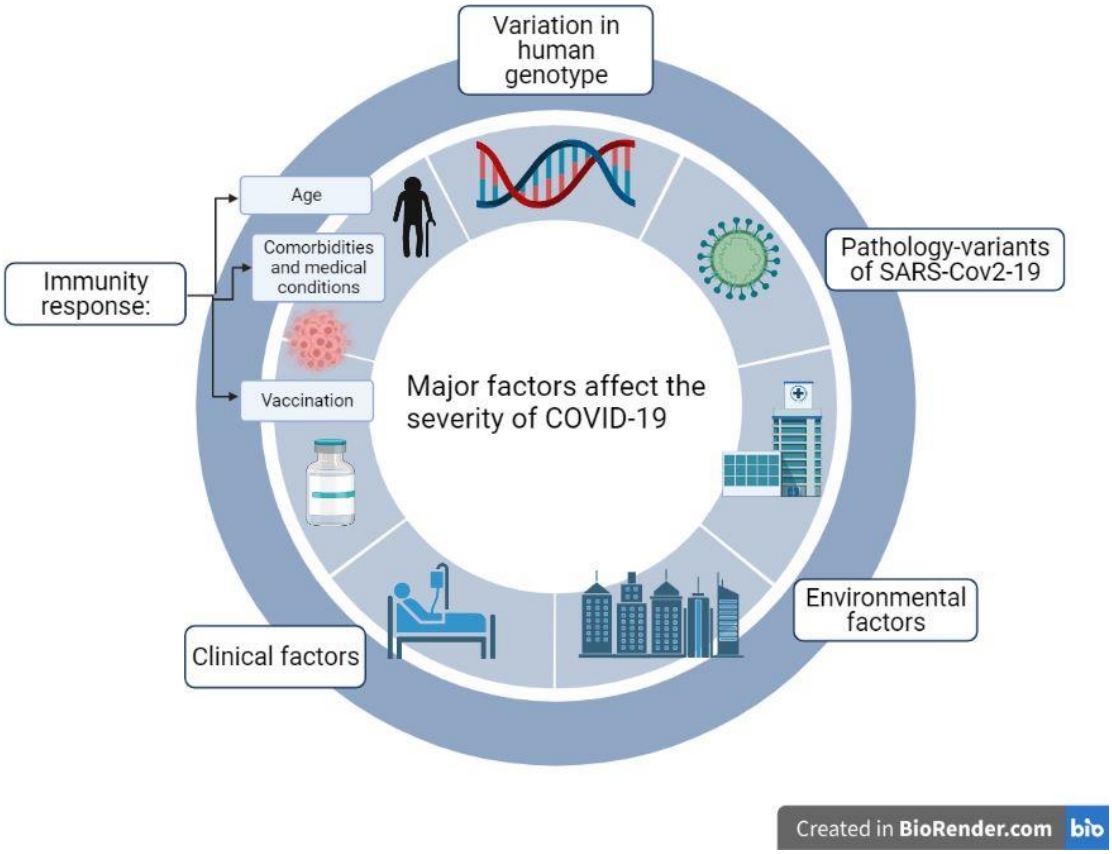

Fig.1: The graphical abstract of this essay. (BioRender.com)

Introduction

Coronavirus have first been discovered is in 1965 with the symptoms similar to common cold, researchers named it after its appearance, clown-like. SARS-Cov2 is genetically similar to SARS-Cov and MERS. Nevertheless, the viral features have are special in SARS-Cov2 The six functional open reading frames (ORFs) are arranged in order from 5′ to 3′: replicase , spike, envelope, membrane and nucleocapsid.(B.Hu et al 2020) Coronavirus has shown its power back in the history about was not as severe as what we are facing today. People around the whole world have been suffering or affected by the virus-caused epidemic for more than two years either because of infection or affected by the isolation system and extremely inconvenient global transportation. Also, the global economy has been influenced on an unprecedentedly large scale. The experts and scientists in many fields are looking for ways to eliminate this pandemic and the medical staff-doctors, nurses and volunteers- are combating this pandemic all the time. However, the statistical information has not shown any drop in the new confirmed cases, this fight between humans and SARS-Cov-2 seems endless and hopeless. As of March 12, 2022, there are cumulative cases of 452,201,564. Cumulative death 6,029,852 (From world health organization Coronavirus (COVID-19) Dashboard). Remarkably, many public articles and clinical observations (J.Mueller et al 2021)(S.Bostan et al 2020)(S.Kaushik et al 2020)(I.Chakraborty and P.Maity) show that people in different regions and conditions show significantly different levels of severity by the expression of their symptoms. Mild cases are marked by the onset of symptoms such as fever, cough, fatigue, shortness of breath, headache, diarrhea, and so forth, without evidence of viral pneumonia or hypoxia. Moderate cases include clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia. Severe cases demonstrate clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) Critical cases present symptoms such as acute respiratory distress syndrome (ARDS), sepsis, and/or septic shock (NCT05175846)

Mild	Moderate	Severe
Fever, cough, fatigue, shortness of breathe, headache, diarrhea	Clinical signs of pneumonia, fever, cough, dyspnea, fast breathing	Clinical signs of pneumonia, fever, cough, dyspnea, fast breathing, ARDS, sepsis(sepsis shock)

This suggests a question: what are the factors affecting the severity of COVID-19?

1.Variation in human genotype

Many articles have found out that one of the major factors that affect the severity of Coronavirus disease (COVID-19) by infected Severe Acute Respiratory Syndrome Coronavirus2(SARS-Cov-2) is the variation in the human genome. Indeed, it is a fact that people from different parts of the world have slightly different gene sequences and it partially explains why we have varying symptoms even we have the same sex, age, and are infected by the same variant. Each genome can influence immune responses differently.There are nine locations of the genome that are relevant to the severity of the COVID-19. However, only two of them relates to the severity of COVID-19, the other related to other capability of the virus such as the transmission. A research group has found that the gene dipeptidyl peptidase 9(DPP9) increases the risk and probability of becoming severe symptoms and critically ill.(Samira Asgari and Lionel A. Pousaz2021)[i] A study shows that in a hospitalized situation, geneDPP9 plays a key role in driven the host to severe innate inflammation specifically in critical lung injury. Eventually driven the patient to a life-threatening condition.The idiopathic pulmonary fibrosis associated with gene DPP9. DPP9 increases the antigen presentation and the activation of inflammation(E.Pairo-Castineira et al 2021)

Another gene involved is HLA. Patients with variant HLA-A*11:01 had a relatively lower capacity to present SARS-Cov-2 antigens compared with other frequent HLA class I molecules, HLA-A*11:01 or HLA-A*24:02 (Yusuke Tomita et al 2020)[ii] The HLA genotypes may cause the T-cell-mediated antiviral response to SARS-Cov-2 limitation, and stimulate the antiviral substances against the infection of SARS-Cov-2, and that could influence the severity and prevalence of COVID-19. Moreover, the HLA genotype class 2 shows a significant downregultion leading to the reduction of several immune cells in severe cases of COVID-19 patients-the patients with ARDS (A.Wiki, A.Rustagi, N.Zhao, et al 2020)[iii]. To the other side of the question, the application. The fact that HLA gene polymorphisms strongly affect the severity of COVID-19 provides us with a brand new idea of vaccination, treatment and clinical application.The gene analysis can take place before the vaccination and with this report, medical staff or hospital can consider which group of people needed to be vaccinated the first.

2. Immune responses

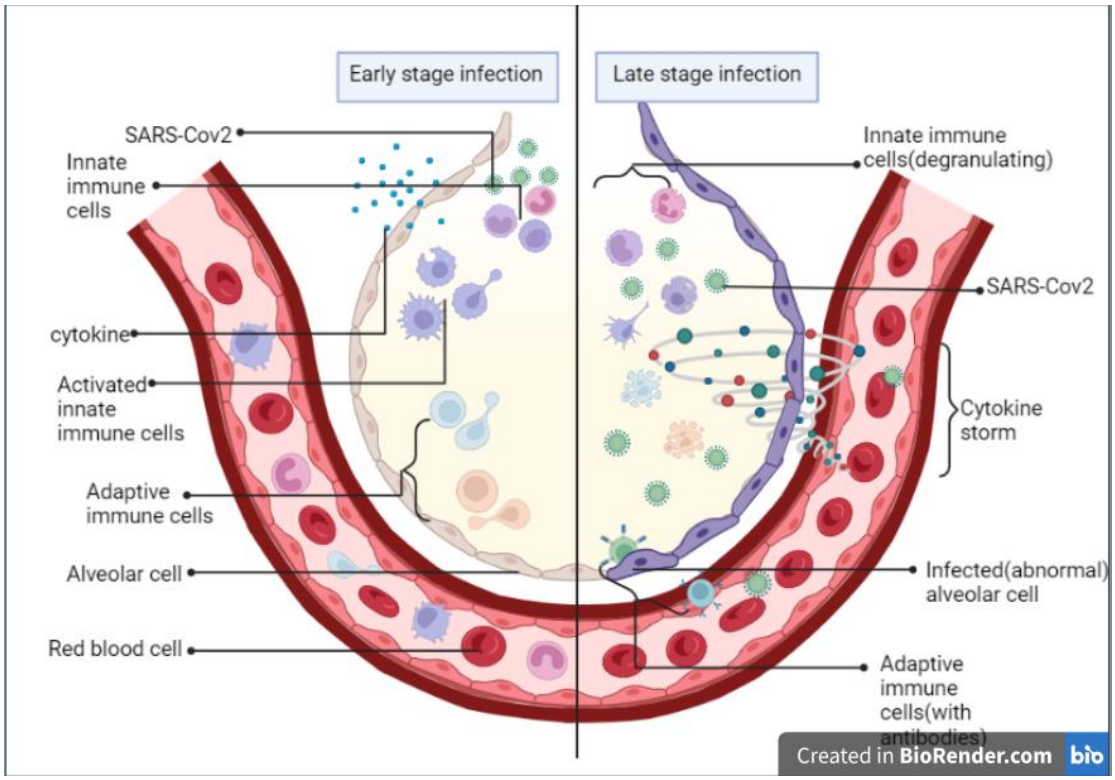

Fig.2: The primary alveolar infection of SARS-Cov2 (BioRender.com) The main purpose of this image is to give readers a clear view about the primary invasion of SARS-Cov2 in alveolar. Additionally give a comparison between the early and late stage of COVID-19.

A brief introduction of the human immune system with SARS-Cov2.

The immune system in our body itself undoubtedly is the best defence system against the infection of SARS-Cov2 since no specific drugs invented. The innate immune cell is the first enemy that SARS-Cov2 needs to fight. These included neutrophils, dendritic cells, natural killer (NK) cells, phagocyte, macrophage. During the fight between the innate immune cells and viruses, the cells also produce the biochemicals such as cytokine and chemokines. They play the role of attracting lymphocytes to the place that requires them. Inflammation is caused by these biochemicals, thus macrophages and neutrophils are involved in this process also called the inflammatory cells. The level of inflammation is relevant to the severity of COVID-19. Mild, moderate, or critical inflammation cause patients to have a slightly different painess. Sometimes it is life-threatening, like the cytokine storm caused by COVID-19(Shown in Fig2.) Another defence system is adaptive immunity. This includes B and T lymphocytes are activated by viral antigens. They are transported

via blood to the infected area. The main job of T-lymphocyte is to engulf the infected cell and further activates B-memory cell meanwhile B-lymphocyte produces the B-cell antigen receptor (BCR) which contributes to the production of antibody. The antibodies has a binding site that specifically binds with the antigen. All the three components play an important role in defence against SARS-Cov2.

1) Age

When the age of the patients with severe conditions increased by five years, the risk increased by 15.25%. (M. Chowdhury, N.Hossain, M.Keshem, et al 2020)[iv]. The severity of COVID-19 in the elderly is much more critical than that in other age groups in most of the time. Thus, it explains why the mortality rate in the elderly is the highest throughout the world in addition to the underlying comorbidities. Previous studies in the field of immunology and serology export that the severity of COVID-19 in elderly patients is related to the type of antibodies and the quantity of them that can be produced in the human body from different age groups. There are several specific antibodies against SARS-Cov2. In general, children and teenagers(K.Selva, et al 2021) have a more intense B-lymphocyte immune response to SARS-Cov2 and the diversity of antibodies is larger than that of the elderly. One explanation due to the observation is that the antibodies' feature of elderly is more specific and more experienced, such as the Cov specific reactor antibody IgA and IgG response. However, in children or adolescents, the main antibody produced by B-lymphocyte and engaging in the fight against SARS-Cov2 is IgM- which is different from the former two antibodies. With more research, the statistics show as the age increases, the features of antibodies like IgA and IgG increase and the type of antibodies like IgM decreases. This correlates with the probability of severe cases increasing as the age increases.

This investigation strongly supports that the younger the person, the stronger the adaptive immune response (K.Selva et al 2021)[v]. That also means they are more non-specific to the virus type. In this case, the adaptive immune functions will be certainly altered due to the difference in carried antibodies. Different age-specific antibodies contributed differently in the same situation, so the speed of the SARS-Cov2 got destroyed differs. In this case, the transmission of the virus is faster in the elderly group, so the chance for the virus to develop critical disease increases. A large proportion of old people died because of the development of the late stage of the COVID-19 like ARDS. As a result, the severity of COVID-19 in the elderly group is higher, correlated with a high mortality rate. Conversely, children and adolescents

may have a higher risk of inflammation because of the more active immune response of the innate immune cells. The cytokine they produce may become large in quantity due to the increase in the viral load. If the cytokine load is too high. The cytokine storm and cytokine release syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation(Shown at Fig2) Moreover, younger people also have more naive T-cells. A naive T cell means the T cell that is mature enough but hasn't encountered any pathogen. This indicates that they have better adaptability in new pathogens, so that for youths, the lymphocytes function is higher than the elderly groups. In this case, COVID-19 will be inhabited on a relatively larger scale. Therefore overall chances for youngsters to develop critical case drops.

2) Comorbidities and underlying medical conditions

Research shows the result that the COVID-19 patients with comorbidities such as diabetes, hypertension, obesity, chronic obstructive pulmonary effect, cardiovascular disease, renal diseases, liver diseases, malignancies, AIDS have a higher risk to develop a clinically critical case. (H.Ejaz, A.Alsrhani, A.Zafar, et al 2020)[vi]. Briefly, 3 main reasons give the explanation : the greater expression of angiotensin-converting enzyme 2 (ACE2) receptors throughout the body, the higher release of cytokine storm, and the weakness of the immune system. First of all, the a greater expression of ACE2 in our body. ACE2 plays a major role in helping SARS Cov2 to enter human cells. More detailed, the protein spike of SARS-Cov2 attaches the ACE2 receptor and entry the cell by endocytosis ACE2 receptor is a membrane-bound aminopeptidase, mostly located at the heart, lungs, cardiovascular system, liver, and kidney in a normal proportionality. However, a few underlying diseases may increase the secretion of ACE2 receptors and other forms of enzymes that may lead to a higher invasion rate of SARS-Cov2 in these regions. As a result, in the situation of the invasion of SARS-Cov2, patients with comorbidities such as aforementioned conditions showed a faster rate in the development of COVID-19. Secondly, the immune cells may be hyperactivated, secrete cytokines, and accumulate cytokine storms in addition to causing critical inflammatory that may be life-threatening to the patients.Thirdly, the immune system might be weakened in a patient with an underlying disease compared to a healthy person. Take malignancy as an example, the major conservative treatments of malignancy are radiotherapy and chemotherapy. The basic chemicals in chemotherapy against tumour are Altretamine, Bendamustine, Busulfan etc. Which leads to a large decline in immune cell activity in addition to the immune response. In another case, people suffering

from HIV/AIDS have a higher risk to infect SARS-Cov2 due to the same reason. Compromised immune system due to HIV infection. Incredibly, HIV＋ patients who taking antiretroviral drugs(ART) commonly have mild disease in COVID-19. It is reasonable to deduce that ART may contribute to the controlling of SARS-Cov2 in some way.(H.Ejaz, A.Alsrhani, A.Zafer, et al) More investigations are required in this aspect as well. Furthermore, the neurostimulator drugs may be considered to be a factor that contributes to the delay of the immune response to correlates with the severity of COVID-19 as well but no further explanations in this passage due to the lack of primary evidence.

S. No.	Disease	Country with mortality %			References
		China	Italy	USA	
1	Hypertension	9.5	73.8	Not reported	[13,41,53]
2	Diabetes	7.4	35.5	58	[13,52,53]
3	COPD	7	13.7	4	[13,32,53]
4	CVD	7.3	42.5	9	[41,53,54]
5	Liver diseases	2.4	3.7	0.6	[[53], [54], [55]]
6	Obesity	13	8.5	55	[15,41,51]
7	Renal diseases	0.7	20.2	21	[13,52,53]
8	Malignancy	2	5	9.5	[15,46,49]

Fig3, diseases and country with percentage mortality. Taken from Ejaz, Hasan Alsrhani, Abdullah et al 2020)

3)Vaccination

Certainly, people with the injection of the vaccine have less incidence than people without any shots (B.Haynes et al 2020) How does vaccination affect patients' severity and hospitalisation mortality? People can be supported in a various way such as giving antibodies straightly or giving the weakened virus(or its RNA) to the body and triggering the memory antibody and cellular responses owing to prior vaccination. To explain the latter, the weakened pathogen will be identified in a short period and the passive immune cells are going to produce the antibodies specific to SARS-Cov-2, however, research shows that one antibody of a variant of SARS-Cov-2 could not cope with other variants(P.Jalkanen et al 2021) When the same pathogen invades again(a new variant) the antibodies and the memory cells

take part in the process. Then this process slows and mitigates the development of SARS-Cov-2 from getting critical cases of COVID-19 to prevent ARDS, fatal organ failure, and even death(M.Tenforde, W.Self, K.Adams, et al 2021)[vii].However, it is artificial passive immunity because humans gained it by injunction. The antibodies might not be lasting in a long time and that is the field of vaccination effectiveness. Relevant clinical research has shown that COVID-19 hospitalisation with reduced likelihood of vaccination(K.Bajema et al 2021) Overall, there is a strong evidence that vaccination can reduce the severity, and it is important to ensure the accessibility to the vaccines by all the world regions to combat the disease worldwide.

3. Clinical factors

The clinical factors such as the infrastructure of hospitalization, use of drugs, and the professionalism of the medical staff like doctors depend a lot on the severity of COVID-19. Firstly, the professionalism of the medical staff. COVID-19 develops incredibly fast into a severe case in some situations. It depends on the personal conditions of the patient like age, the effectiveness of the immune system, etc. So that the clinical doctors' judgement and actions play an essential role in whether the development of severity is being controlled or accelerated. Secondly, as mentioned previously, special prevention required in the patients with comorbidities deteriorates COVID-19. Thirdly, the hospital facilities and the use of drugs, because nowadays there do not exist any virus medicine specific to SARS-Cov-2 that COVID-19 patients can rely on. The substitute drugs might be used instead such as Redeliver which initial purpose is to cure Ebola outbreak(J.Pardo et al 2020) In this case, the side effects of this kind of drug should to be added into consideration. Moreover, lots of regions in the world have insufficient medical instruments and are deficient in drugs so the patients in these regions or countries have inadequate medical treatment. Therefore, more medical help might be needed in those developing countries. That might be a part of the work of WHO.

4. Pathology- Variants of SARS-Cov-2

Another factor that is essential to mention is the variants to SARS-Cov2. The variants of SARS-Cov-2 all have different characteristics and specialisation in each aspect. From December 2019 to now, SARS-Cov2 has developed into several variants. Interestingly, different variants lead to different severity of the patients and one host

may carry various variants of SARS-Cov-2. Besides, different variants differ significantly in transmission capacity and COVID-19 severity. The pathology of it is the genetic variability that correlates with the S protein and the affinity between the protein and human ACE2 receptors.The mutation of the variants help the SARS-Cov-2 have better interaction with ACE2 receptor. This helps the virus established faster in the propagate infection. Additionally causes more severe cases(C.van Oosterhout 2021) The 1,273-amino acid trimeric glycoprotein from the spike protein of SARS-Cov2 is a main helper for the virus entry the human host cell. In addition more viral features like the other protein spikes and the receptor-binding domain(RBD) also lead to the severity of COVID-19.

5. Environmental factors

The first thing that needs to be considered is the demographic reasons, that is how fast can patients get professional medical support and treatment as soon as possible and how fast government react to it. The development of a pandemic metropolis is extremely fast(H.Eslami and M.Jalili 2020) a breakout may happen everywhere and anytime. Thus, throughout society, the medical staff, government workers, and the public should all make an effort and spend time and attention in this worldwide pandemic. Secondly, the natural environment of a country can lead to a slight difference in the portion of the population that has severe cases of COVID-19. For instance, the country or region which has a vast population of comorbidity patients due to its poor natural environment may have a higher risk in high mortality of COVID-19 and large prevalence. Many diseases are induced by the external environment like photochemical pollution ore cancergens and a country's natural environment directly determines that the distance between people and these bad factors lead to the underlying diseases lead to more severe COVID-19. However, to ameliorate this is a sort of long-term strategy that may lead to hundreds of other concerns such as economic decline. So that the help from developed countries, WHO, and United Nations is required.

Conclusion

To be concluded, the review explains different levels of severity of COVID-19 and at least five factors affecting it. The variation in human genome, immune responses, pathology of variants, clinical factors and environmental factors. These five factors lead to convincing reasons for the development of SARS-Cov-2 and the severity of

COVID-19. Apparently, more research needed to be done in the clinical medicine, pathology and genetics in order to fully developed all the relevant factors such as the underlying genes or mutations that the host has lead to make the disease less harmful. It is reasonable to assume that in reality, more factors determine the severity of this disease. Like gender or geological variation(extreme climate) As far as I am concerned, about the variation of the genotype in human, a more sophisticated system of vaccination should be developed so that it will be able to benefit both public and economy. Furthermore, the whole world does not ready for the next mutation of this unpredictable virus, maybe it will be fatal. So the antiviral drugs and vaccinations should be more tolerate and experts need to consider this as an issue

Abbreviation

(i) COVID-19: Coronavirus disease.

(ii) SARS-Cov-2: Severe acute respiratory syndrome coronavirus-2

(iii) WHO: World health organization

(iv) SpO2: oxygen saturation

(v) ARDS: Acute respiratory distress syndrome

(vi) HLA: Human leukocyte antigens

(vii) NK: Natural killer (cells)

(viii) BCR: B-cell antigen receptor

(ix) IgA: ImmunoglobulinA

(x) IgM: ImmunoglobulinM

(xi) IgG: Immunoglobuling

(xii) ACE2: Angiotensin-converting enzyme 2

(xiii) CVD: Cardiovascular disease

(xiv) COPD: Chronic obstructive pulmonary disease

(xv) HIV: Human immunodeficiency virus

(xvi) AIDS: Acquired immune deficiency syndrome

(xvii) ART: Antiretroviral drugs

(xviii) RBD: Receptor-binding domain

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