Literature Review

Effect of viral, reservoir, host and environmental factors on morbidity and mortality of COVID-19 disease

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ABSTRACT

The COVID-19 pandemic has been going on for more than 2 years. The number of patients with the disease continues to increase as well as those who die. The number of cases of illness and death is different in each country and even varies in one country in certain seasons and in certain ethnic groups. This virus also always creates new variants that have different virulence, so that it can prevent the transmission of the COVID-19 virus. Virus evolution triggers the emergence of new virus strains and these new variants cause different morbidity and mortality. Other factors thought to support the evolution of the virus are reservoir, host immunity, extreme environmental conditions. This is supported by the different percentages of morbidity and mortality in different countries. This study aims to determine the effect of the factors that influence the level of morbidity and mortality in terms of virus, reservoir, host, and environmental aspects.

Keywords **:** COVID-19, variant, evolution, morbidity, mortality
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INTRODUCTION

The COVID-19 pandemic emerged due to the corona virus which was first detected in the Chinese city of Wuhan at the end of 2019 (Jia & Gong, 2021). Bats are considered to be the reservoir of the virus. SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2) is the virus that causes COVID-19 (da Silva et al., 2021). The sequence of the first corona virus cases in China (in December 2019) was found to be different in several countries during the pandemic process. This difference indicates that the virus undergoes mutations and gives rise to new variants (Banoun, 2021). Variant B.1.1.7 is found in the UK, B.1.351 in South Africa and P.1 in Brazil (Jia & Gong, 2021). Some researchers and journals estimate that this virus has spread and mutated even before the pandemic appeared, for example Journal of Li et al in 2020 based on an analysis of the alleged spread of this virus in early October 2019 or even earlier before the first case of COVID-19. Sallard et al. in 2020 describes the various possibilities to determine the origin of the virus whether natural or artificial based on the molecular phylogenetic, sequence, and function of the structural protein of the coronavirus. Some researchers concluded that there was a time between the circulation of the virus and the cause of the emergence of the virus evolving and mutating but it was not detected because at that time the virus was not yet a disease (Banoun, 2021).

Virus characteristic

The COVID-19 virus belongs to the Coronaviridae family and is named SARS-CoV-2 because of its 79% similarity in genome structure to the 2003 SARS-CoV virus. (Ha, John, & Zumwalt, 2021). Coronaviruses are family of enveloped positive-sense RNA viruses (V'kovski et al., 2021). RNA viruses have the ability to replicate and evolve rapidly, which causes the emergence of new variants continuously (Jaag & Nagy, 2010)**.** The ability of these RNA viruses to trigger an increase in mutations of up to a million times and these mutations correlate with increased virulence and evolutionary ability (Duffy, 2018). One of the evolutionary capabilities of RNA viruses is the ability to recombine RNA. This ability also facilitates viruses to attack new reservoir or host species, increases virus resistance, and forms new strains/variants (Jaag & Nagy, 2010) (Duffy, 2018).

These variations/mutations cause different levels of infectivity. In Europe from March to April, there was a decline in the number of people with and deaths from the virus. The virus is thought to have evolved into a benign strain since late May 2020 (Banoun, 2021). Three viral components identified as contributing to the virulence and pathogenicity of SARS-CoV-2 (Alsobaie, 2021):

1) RBD protein S

The receptor-binding domain (RBD) on the SARS-CoV-2 S protein must bind to the host cell ACE2 receptor for docking and entry. Binding between RBD and ACE2 is the initial stage of virus transmission from one species to another (da Silva et al., 2021). The SARS-CoV-2 S protein has a stronger binding affinity compared to other coronaviruses that have been caused by previous outbreaks (SARS-CoV and MERS-CoV) so that the morbidity and mortality rates caused by SARS-CoV-2 are also higher during the pandemic (Alsobaie, 2021).

2) Different types and functions of accessory proteins and nonstructural proteins

Accessory proteins ORF33a, ORF8b, ORF6, and E play a role in the innate immune system, namely the NLRP3 inflammasome which triggers the secretion of proinflammatory cytokines. There are many protein accessories whose function are not yet known (Alsobaie, 2021). The role of nonstructural proteins can be seen in table 1 (Hidalgo, Valdés, & González, 2021).

3) polybase cleavage site

The addition of polybase sites at the S1 and S2 junctions can alter the virulence of the virus, but it has not been shown whether it increases or decreases SARS-CoV-2 transmission (Alsobaie, 2021).

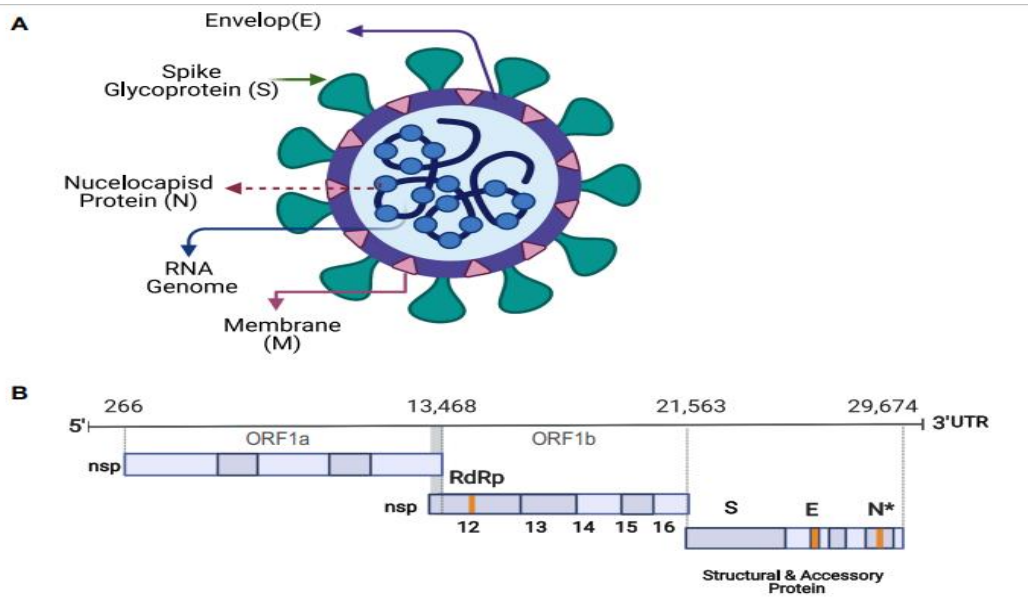

Figure 1 (A) SARS-CoV-2 illustration. (B) open reading frame (ORF)1a/b composed of 16 non-structural proteins (nsp1–16) and RNA-dependent RNA polymerase (RdRp) (Alsobaie, 2021).

Table 1. Functions of coronavirus nonstructural proteins

Protein	Functions
Nsp1	Host mRNA degradation; translation inhibition; cell cycle arrest; inhibition of IFN signaling
Nsp2	Unknown
Nsp3	Papain-like proteases (PL1pro, PL2pro); poly(ADP-ribose) binding; DMV formation; IFN antagonist; nucleic acid binding; deubiquitinating activity
Nsp4	DMV formation
Nsp5	Main protease (Mpro, 3CLpro)
Nsp6	DMV formation
Nsp7	Single-stranded RNA binding
Nsp8	Primase
Nsp9	Part of replicase complex
Nsp10	Part of replicase complex
Nsp11	Unknown
Nsp12	RNA-dependent RNA polymerase
Nsp13	Helicase; RNA 5′-triphosphatase activity
Nsp14	3′ - 5′ exoribonuclease; (guanine-N7)- methyltransferase
Nsp15	Endonuclease
Nsp16	2′O-methytransferase

(Hidalgo, Valdés, & González, 2021)

The emergence of new variants was triggered by two factors, are the low fidelity of RNA-dependent RNA polymerase (RdRp) and the high ability of RNA recombination. Corona virus has a high mutation rate due to its low RdRp precision. The extremely high mutation rate gives the coronavirus the ability to evolve according to new environmental stresses and changes, i.e. adapt to different types of environments. In the case of coronavirus, mRNA synthesis occurs discontinuously, replicative RNA complexes are located within the genome and high template turnover during replication triggers recombination events. All these factors give more plasticity to evolve (da Silva et al., 2021). The mutation rate of viruses is much higher than that of other organisms. this ability is especially true in RNA viruses such as SARS-CoV-2 because the hydroxyl group in the genome serves as a catalytic group for

mutations. This high mutational ability in COVID-19 affects virus virulence and is able to make the virus more virulent than the initial COVID-19 strain. The molecular epidemiology approach provides researchers with the opportunity to determine specific variants and integrate their transmission. It can be an important tool in controlling outbreaks (Ansori et al., 2020)**.**

Reservoir

Bats are animals that were first suspected of being a reservoir of the corona virus. This virus is carried by reservoirs and transmitted to humans or other animals that have close contact with humans (pets or pets for consumption of food sold in the Chinese market) (Valencak et al., 2021). Genetic viral mutations occur during the transmission process in animals and produce new variants through recombinant mechanisms. This new variant is able to adapt and cross species boundaries. Genetic mutation in RBD protein S, polybasic sites, functional roles of accessory proteins play a role in transspecies transmission (Alsobaie, 2021) and this happened in the case of the SARS-CoV and MERS-CoV pandemics (Wu, Chen, & Chan, 2020) (Shereen et al., 2020).

The coronavirus isolated from the Malay pangolin had amino acid similarities in E, N and S proteins by 100%, 98.6%, 97.8%, and 90.7% when compared to SARS-CoV-2 (Xiao et al., 2020). Another study found that SARS-CoV-2 RBD amino acid similarity to pangolin coronavirus was higher (97.4%) bat coronavirus (89.2%) (da Silva et al., 2021). This information suggests that pangolins may be an intermediate reservoir for SARS-CoV-2 (Xiao et al., 2020).

Some data have found that SARS CoV-2 infects mammals and other bird species, including livestock and pets (V'kovski et al., 2021). Data show that there are types of animals infected with SARS CoV-2, but not all infected species are symptomatic (da Silva et al., 2021). Some data have found that SARS-CoV-2 can replicate and cause symptoms in ferrets and cats and is transmitted through the respiratory tract but the virus does not replicate in dogs, pigs, chickens, and ducks (Shi et al., 2020). Infected animals can play a role in triggering new strains of the virus and possibly spreading these new strains to other people or animals (Valencak et al., 2021). A study in 2021 found that mink infected with the virus by humans or other reservoir animals can transmit the virus back to humans (Prince et al., 2021). The above report indicates that mammals are the species most likely to bridge the entry of the COVID-19 virus in humans. This information can be a strategy to prevent future transmission of COVID-19 and other corona viruses (Rothan & Byrareddy, 2020)**.**

Host (human)

COVID-19 infection has spread globally but countries in Europe and America have higher rates of morbidity and mortality from December 2019 to April 2020 (European center for disease prevention and control, 2020) (Garg et al., 2020) (Sarangarajan et al., 2021). Differences in mortality and morbidity in various ethnicities indicate that the infectivity of the COVID-19 virus is different in certain ethnicities (Ha et al., 2021). Several studies have attempted to analyze host factors that influence differences in the number of COVID-19 morbidity and mortality among certain populations (Sarangarajan et al., 2021).

A person infected with COVID-19 cannot transmit the virus directly to other people. The infectious dose of COVID-19 is still unclear, but the viral load of the infected patient's sputum is 10^8 copies/mL. Viral load increases at the onset of infection up to 12 days after the onset of symptoms so that COVID-19 positive patients can transmit the virus for about 2 weeks after initial symptoms appear (Wu et al., 2020). Angiotensin-converting enzyme 2 (ACE2) is the main receptor that binds to the COVID-19 virus and infection causes decreased ACE2 expression. The binding of COVID-19 to ACE2 may enhance the response to ACE and Angiotensin II signaling and is further enhanced by the presence of genetic polymorphisms in ACE where the effect is on COVID-19 symptoms. The presence of ACE polymorphisms in certain ethnic groups that play a role in increasing morbidity and mortality in these ethnic populations due to COVID-19, for example in the African-American race (Sarangarajan et al., 2021). Comparative rates of COVID-19 infection in the main black country are three times higher than in the white largest country (Ha et al., 2021). An in silico study examining the variability of human ACE2 found polymorphisms that could make these individuals more susceptible or protect them from SARS-CoV-2. The variants of ACE2 polymorphism that increase the affinity of ACE2/S-protein are S19P, I21V, E23K, K26R, K26E, T27A, N64K, T92I, Q102P, M383T. The variants of ACE2 polymorphism that decrease the affinity of ACE2/S-protein and are thought to be protective polymorphisms, namely K31R and E37K (Suryamohan et al., 2021).

This difference in the severity of the disease can be caused of the individual's immune system (Banoun, 2021). Several studies have explained the relationship between immunogenicity and individual resistance to emerging new variants (Alsobaie, 2021).

A study showed that the presence of antibodies provided cross-protection with early case COVID-19 strains but protection was slightly reduced in variants B.1.1.7 and B.1.351 (Sebai & Mir, 2020). Sex differences provide different immunity where the X chromosome is associated with the gene coding for adaptive and innate immunity. Women who have an XX chromosome allow for a stronger immune response than men who don't have a "spare" X chromosome. This makes women have stronger immunity while men tend to be more susceptible to pathogens. Differences in immunity between sexes are also influenced by differences in sex hormones. Some immune cells have varying amounts of sex hormone receptors; women show a higher number of receptors than men. Gender was not associated with ACE2 expression levels although more men were infected and died by SARS-CoV-2 during the pandemic (Ha et al., 2021). ACE2 expression correlates with age i.e. increases in renin-angiotensin II signaling with age. This can exacerbate COVID-19 symptoms in the elderly (AlGhatrif et al., 2021). Morbidity and mortality increase in individuals aged > 50 years, especially individuals with comorbid hypertension, obesity, and diabetes (Sarangarajan et al., 2021).

Viral proteins that trigger the host immune response continue to mutate. Host immunity is triggered to overcome the new viral strain. People who are exposed but whose immune system does not fight the virus effectively will become seriously ill. This differs in those who are exposed but not because the immune system destroys the infecting virus or is able to induce disease in a less efficient (replicated less efficiently) form of the virus. This

mechanism is predicted to be one of the factors causing the mild severity of the symptoms of a disease (Banoun, 2021). One of the efforts to stop a pandemic is to obtain groups that have the highest immunity among the population through natural immunity or vaccines which are very important to prevent and reduce infectious diseases, and stop the evolution of viruses (Alsobaie, 2021).

Environment

Season and rainfall

Seasons play a role in viral mutation. Epidemiological analysis of the SARS-CoV-2 genome found that the rate of spread and evolution of the virus is lower in summer than in other seasons because high summer temperatures affect virus viability (Jia & Gong, 2021). This is also seen in Australia where the incidence in winter is six times higher than in summer (Kifer et al., 2021). The more varied the environment experienced by the RNA virus, the lower the resistance of the virus in that environment but the higher the mutation rate triggered so that the virus can adapt to that environment. Mutations of this virus can increase or decrease the virulence of the virus (Duffy, 2018)**.** Seasonal changes also affect individual susceptibility, namely the interaction between changes in temperature and dysfunction of airway defense mechanisms that lead to an increased incidence of viral infections and a higher susceptibility to the nasal mucosa under conditions of low temperature and humidity (McMullin et al., 2019). Breathing air with low humidity will reduce the mucociliary transition time of the nose thereby prolonging viral exposure to the nasal mucosa (Kifer et al., 2021). Rainfall is an important factor to consider. Countries that have high rainfall show an increase in the number of positive COVID-19 patients, with an additional 56.01 cases / inch increase in average rainfall / day (Saputra, Susanna, & Saki, 2021).

Temperature

Cities with temperatures higher than 25^0 C experience a decrease in the number of positive COVID-19 cases (Mozumder et al., 2021). This suggests that the increase in temperature contributed to the easing of the outbreak (Saputra et al., 2021). Rising temperatures increase the number of positive COVID-19 cases in Pakistan (Basray et al., 2021). The same thing happened in Oman, United Arab Emirates, Qatar (Meo et al., 2020). This proves that there are other factors besides the influence of temperature that trigger an increase in COVID-19 transmission, namely human mobility. Increased human mobility can support the spread of disease if a person carries the disease or acts as a carrier (Findlater & Bogoch, 2018).

Sunlight

Ratnesar-Shumate et al found that ultraviolet (UV) B sunlight can inactivate viruses in aerosols rapidly (Saputra et al., 2021). Corona virus virulence decreased by 90%/6.8–12.8 min of UV B exposure time (Schuit et al., 2020)**. S**unlight can be used to reduce the risk of transmission from aerosols (Azuma et al., 2020)**.**

Materials around the environment

The COVID-19 virus only survives 4 hours on copper surfaces. This has led to the use of copper in metal combinations as a strategy to reduce the risk of transmission. Copper ions can destabilize proteins in viruses and have the effect of inactivating viruses by causing aggregation of viral particles (Azuma et al., 2020).

Wildlife habitat

Deforestation and ecosystem changes that result in the destruction of viruses in nature and encourage the evolution of viruses to adapt to new environments are the basis of the zoonotic process (da Silva et al., 2021). Continuous habitat destruction by humans and animals will cause al zoonotic events (Prince et al., 2021). Continuous monitoring of wildlife at the urban-rural boundaries, trade, livestock and food distribution is needed to prevent further epidemics from appearing (da Silva et al., 2021).

Water and wastewater

The COVID-19 virus was detected and can survive in wastewater (Eslami & Jalili, 2020). RNA viruses can be found in the mucus, phlegm, blood and feces of COVID-19 patients and all of these are included in medical waste (Wu et al., 2020). Insects using medical waste technology can act as reservoirs and infect other species. Virus adaptation in new reservoirs can induce new variants and complicate the prevention of COVID-19 transmission. This can be used by improving environmental hygiene, such as putting waste into bags and landfills, controlling disposal, sanitation of toilets, and a good waste disposal system (Eslami & Jalili, 2020).

Conclusion

Many factors from the virus, reservoir, and host as well as the environment can trigger viral mutations and alter virulence so that it can increase or decrease the number and mortality from COVID-19. Epidemiological approaches and biomolecular research are needed to control the causative agents (viruses, bacteria, etc.), reservoirs, humans and the environment to prevent new pandemics from occurring in the future.

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