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LITERATURE REVIEW

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

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ABSTRACT

The COVID-19 pandemic has been going on for more than two years. The number of sufferers of this disease continues to increase as well as those who die. The number of disease and death cases varies in each country and even in one country in certain seasons and certain tribes. This is triggered by the evolution of viruses that create new variants with different virulences so that they can affect the transmission of the COVID-19 virus. Several factors can trigger the evolution of the virus, one of which is the ability to mutate to create new variants and/or new strains that cause differences in morbidity and mortality due to early COVID-19 strains. Other factors that favor viral evolution are the reservoir, host immunity, and extreme environmental conditions. This is supported by differences in the percentage of morbidity and mortality in various countries. This literature review aims to determine the effect of viral, reservoir, host, and environmental factors (season and rainfall, temperature, sunlight, materials around the environment, animal habitat, water, and wastewater) on the evolution of viruses that affect morbidity and mortality in COVID-19 disease.

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INTRODUCTION

The COVID-19 pandemic emerged due to the coronavirus, which was first detected in the Chinese city of Wuhan at the end of 2019 (Jia & Gong, 2021). This coronavirus is a zoonotic type, and bats are considered the first reservoir of the virus. The virus that causes COVID-19 is called SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) (da Silva et al., 2021). The morbidity and mortality of the first coronavirus case in China (in December 2019) were different in several countries during the pandemic. This difference indicates that the virus mutates 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 had spread and mutated before the pandemic emerged. Several studies in 2020 analyzed the alleged spread of this virus in early October 2019, or even earlier, before the first cases of this virus appeared. The circulation of this virus was accompanied by the evolution and mutation of the virus. Still, the virus was not detected because, at that time, the virus had not yet caused disease (Banoun, 2021).

The time required for the evolution of the virus into a virus that is pathogenic to humans and causes the disease is still not known. However, an epidemiological approach can explain what factors can trigger the evolution of a virus to become more dangerous or not. Control of these factors can prevent future outbreaks and reduce morbidity and mortality when an epidemic occurs. These factors are viral, host, reservoir, host, and environmental.

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 a 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 reservoirs 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 have been 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's ACE2 receptor for docking and entry. The 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

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compared to other coronaviruses caused by previous outbreaks (SARS-CoV and MERS-CoV), so 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. Many protein accessories' functions are unknown (Alsobaie, 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).

The illustration of SARS-CoV-2 below shows the shape pattern of the virus in relation to the role of viral components in viral pathogenicity. The SARS-CoV-2 viral RNA complex also triggers a high virus mutation rate.

The emergence of new variants was triggered by two factors: the low fidelity of RNA-dependent RNA polymerase (RdRp) and the high ability of RNA recombination. Coronavirus has a high mutation rate due to its low RdRp precision. The extremely high mutation rate allows the coronavirus to evolve according to new environmental stresses and changes, i.e., adapt to different 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

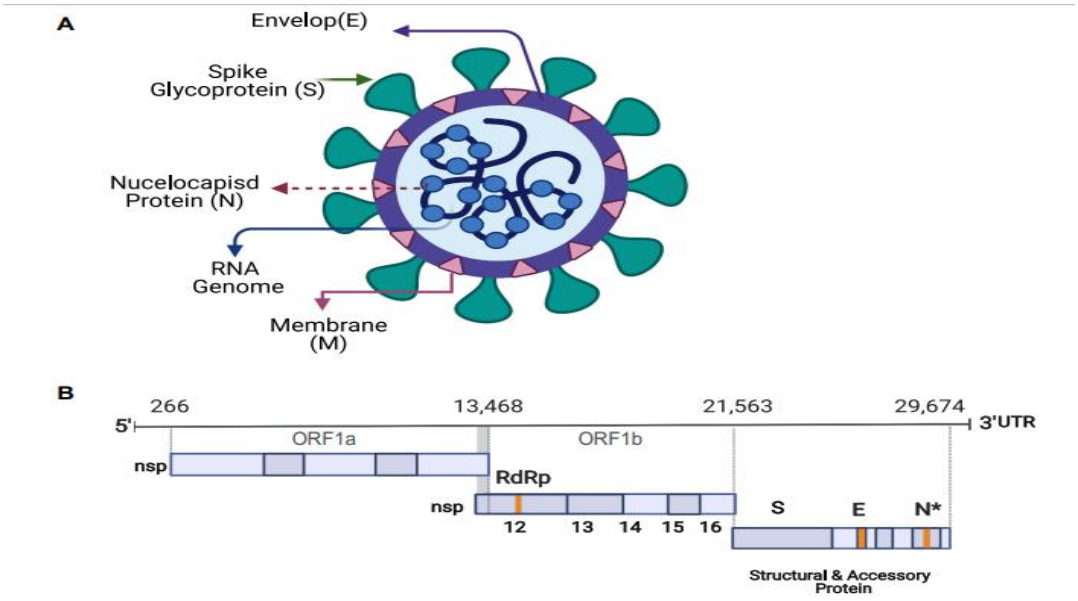

Figure 1. (A) SARS-CoV-2 illustration. (B) the open reading frame (ORF)1a/b is composed of 16 non-structural proteins (nsp1–16) and RNA-dependent RNA polymerase (RdRp) (*Source*: Alsobaie, 2021).

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

Reservoir

Bats are animals that were first suspected of being a reservoir of the coronavirus. 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 can adapt and cross species boundaries. Genetic mutation in RBD protein S, polybasic sites, and functional roles of accessory proteins play a role in trans-species 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% 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 trigger new strains of the virus and possibly spread 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 coronaviruses (Rothan & Byrareddy, 2020).

Host (human)

COVID-19 infection has spread globally, but Europe and American countries had higher morbidity and mortality rates from December 2019 to April 2020 (European Centers 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 tried to analyze the host factors that influence differences in the morbidity and mortality of COVID-19 among specific populations. They can even prevent the spread of new virus variants (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 COVID-19-positive patients can transmit the virus for about two weeks

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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 genetic polymorphisms in ACE, where the effect is on COVID-19 symptoms. The presence of ACE polymorphisms in certain ethnic groups plays 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 largest white 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, and M383T. The variants of ACE2 polymorphism that decrease the affinity of ACE2/S-protein 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 by the individual's immune system (Banoun, 2021). Several studies have explained the relationship between immunogenicity and individual resistance to emerging new variants (Alsobaie, 2021).

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 (Garcia-Beltran et al., 2021). Sex differences provide different immunity where the X chromosome is associated with the gene coding for adaptive and innate immunity. Females with an XX chromosome allow for a stronger immune response than males who do not have a "spare" X chromosome. This makes females have stronger immunity, while males 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; females show a higher number of receptors than males. Gender was not associated with ACE2 expression levels, although more males 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, especially those 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 with the highest immunity among the population through natural immunity or vaccines, which are very important in preventing and reducing infectious diseases, and stopping the evolution of viruses (Alsobaie, 2021).

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Environment

Changes in the environmental factors studied can disrupt the stability of the virus so that it can trigger the evolution of the virus or can kill the virus. Environmental factors that contribute to the mutation (evolution) of the COVID-19 virus are season and rainfall, temperature, sunlight, materials around the environment, wildlife habitat, water, and wastewater.

Season and rainfall

Seasons play a role in viral mutation. Epidemiological analysis of the SARS-CoV-2 genome found that the virus's spread and evolution rate 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 virus's resistance 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 its virulence (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 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 with high rainfall show an increase in 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 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, and Qatar (Meo et al., 2020). This proves that other factors besides the influence of temperature 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). Coronavirus virulence decreased by 90%/6.8–12.8 min of UV B exposure time (Schuit et al., 2020). Sunlight can 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

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will cause all 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 (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 creating a good waste disposal system (Eslami & Jalili, 2020).

CONCLUSION

This literature review aims to determine the effect of viruses, reservoirs, hosts, and environmental factors (season and rainfall, temperature, sunlight, materials around the environment, animal habitats, water, and wastewater) on the evolution of viruses that affect morbidity and mortality of COVID - 19 diseases. Factors from the virus, reservoir, host, and environment can trigger viral mutations and alter virulence to increase or decrease the morbidity and mortality of COVID-19. Epidemiological approaches and biomolecular research are needed to control the causative agents (viruses, bacteria, etc.), reservoirs, humans, and the environment to prevent the occurrence of new pandemics in the future.

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