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Virulence of Mutated SARS-CoV-2 and Susceptibility of COVID-19 Patient: A Literature Review

Alfian Nur Rosyid[1,5], Arina Dery Puspitasari[2,5], Tamara Nur Budiarti[3], Herley Windo Setiawan[1,5], Anggraini Dwi Sensusiati[4,5], Muhammad Amin[1,5]

[1] Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia

[2] Faculty of Pharmacy, University of Airlangga, Surabaya, Indonesia

[3] Faculty of Public Health, University of Airlangga, Surabaya, Indonesia

[4] Department of Radiology, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia

[5] Airlangga University Hospital, Surabaya, Indonesia

Abstract: COVID-19 originated from a pneumonia case with a mysterious cause in Wuhan, China. The spread of the disease is increasingly widespread until WHO declares a pandemic COVID-19 in March 2020. The case increase in human to human continues to occur in almost all world regions until today. SARS COV-2 virus mutations were reported to occur in several countries. This review aims to determine the virulence of mutated SARS-CoV-2 and human susceptibility to virus infection. We discussed the viral origin, pathogenesis, transmission to the host body, risk factors for viral information, infection symptoms, mutations, and examinations performed to support disease diagnosis. Modifications of the SARS-COV-2 virus occur in one or more virus components, i.e., Spike Protein (S), Envelope (E), Membrane Glycoprotein (M), and Nucleocapsid (N). Currently, mutations D.6.1.4.G, B.1.1.7, R203K, and B.1.1.28 are found. This mutation is related to the ease with which a person becomes infected with COVID-19. The level of host susceptibility was influenced by groups of ACE2, TMPRSS2, CTSB, and CTSL. The risk factor of COVID-19 is higher in people with comorbid; each infected person's symptoms can be different. The new mutations of SARS-CoV-2 have been found more virulent and dangerous in several countries around the world. The real-time reverse transcription-polymerase chain reaction (rRT-PCR) examination is required for the primary diagnosis of COVID-19.

Keywords: COVID-19, virulence, susceptibility, SARS-COV-2, mutation, infection disease.

变异非典-冠状病毒-2 的毒力及新冠肺炎患者易感性:文献综述

摘要：新冠肺炎起源于中国武汉的一例具有神秘原因的肺炎病例。在 2020 年 3 月世卫组织宣布新冠肺炎大流行之前，这种疾病的传播越来越普遍。人与人之间的病例增加继续发生在世界几乎所有地区，直到今天。据报道，非典冠状病毒-2 病毒突变发生在几个国家。 本综述的目的是确定突变的非典-冠状病毒-2 的毒力和人类对病毒感染的易感性。我们讨论了病毒起源，发病机制，传播到宿主体内，病毒传播的危险因素，感染症状，突变以及为支持疾病诊断而进行的检查。非典-冠状病毒-2 病毒的突变发生在一种或多种病毒组分中，即穗蛋白（秒），包膜（乙），膜糖蛋白（米）和核衣壳（N）。目前，突变 D.6.1.4。G，乙

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About the authors: Alfian Nur Rosyid, Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia; Airlangga University Hospital, Surabaya, Indonesia; Arina Dery Puspitasari, Faculty of Pharmacy, University of Airlangga, Surabaya, Indonesia; Airlangga University Hospital, Surabaya, Indonesia; Tamara Nur Budiarti, Faculty of Public Health, University of Airlangga, Surabaya, Indonesia; Herley Windo Setiawan, Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia; Airlangga University Hospital, Surabaya, Indonesia; Anggraini Dwi Sensusiati, Department of Radiology, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia; Airlangga University Hospital, Surabaya, Indonesia; Muhammad Amin, Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia; Airlangga University Hospital, Surabaya, Indonesia

.1.1.7，电阻 203 钾和乙.1.1.28 中找到。这种突变与一个人感染新冠肺炎的容易程度有关。宿主易感性的水平受到高手 2，TMPRSS2，CTSB 和 CTSL 水平的影响。新冠肺炎的风险因素在合并症患者中较高;每个感染者的症状可能不同。非典-冠状病毒-2 的新突变已被发现在世界各地的几个国家更具毒性和危险性。新冠肺炎的初级诊断需要实时逆转录-聚合酶链式反应（逆转录聚合酶链反应）检测.

关键词：新冠肺炎，毒力，易感性，非典-冠状病毒-2，突变，感染疾病.

1. Introduction

Towards the end of 2019, pneumonia with a mysterious cause occurred in Wuhan, China. Transmission cases have increased rapidly until WHO (World Health Organization) declared the case as a global COVID-19 pandemic in March 2020. The Director-General of WHO stated that the COVID-19 is pandemic based on the increase of patients numbers significantly in the past two weeks to March 11, 2020. The cases 13-fold increase outside China, and countries with COVID-19 cases increased three times [1].

Transmission of the virus has initially allegedly come from animals to the human who performs contact at one fish market in Wuhan and assumes that place as origin virus. However, some research could not make sure the beginning of the viral transmission. A further investigation said that the virus could spread from human to human. Human-to-human transmission has occurred since mid-December 2019 and increasing up until now [2,3].

Based on the research recommendations, on January 12, 2020, WHO announced the virus's name that causes pneumonia cases in Wuhan as a 2019 novel coronavirus (2019-nCoV) [4]. 2019-nCoV has the same genetic structure as SARS-CoV (Corona Virus), which causes an outbreak of SARS (Severe acute respiratory syndrome), and MERS-CoV, which causes an explosion of MERS (Middle East Respiratory Syndrome). Hence, researchers conclude that SARS-CoV-2 is still in one family with both the virus [5,6]. According to WHO's conclusive data, until March 7, 2021, SARS-CoV-2 has infected more than 115 million patients in the world [7].

SARS-CoV-2 has higher rates of transmission, pathogenesis, and infection than SARS-CoV and MERS-CoV. Spreading viruses become more aggressive because direct communication occurs from human to human. SARS-CoV-2 transmission source becomes from suspects COVID-19's droplets that come out by coughs or sneezes, close contact with suspect COVID-19, and probably spread through fecal-oral [2,8,9]. This paper aims to determine the virulence of SARS-CoV-2 and human susceptibility to virus infection based on these problems. This literature review hypothesizes that the mutation of the SARS-CoV virus-2 will easily infect a susceptible host that was previously lacking. This SARS-CoV-2 mutation may influence new infection, reinfection, including in patients post COVID-19 vaccines.

2. Methods/Materials

SARS-CoV-2 is viruses from the order Nidovirales and the Coronaviridae family. In the Coronaviridae family, this virus is included in the Coronavirinae subfamily. Subfamily Coronavirinae consists of four genera namely Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. SARS-CoV-2 are members of Betacoronavirus genes with another virus, including SARS-CoV and MERS-CoV [5].

The SARS-CoV-2 genome structure was a resemblance sequence of 96,2 % with coronavirus that infects bats. There was phylogenetic relations proximity between bat Coronavirus (BatCoV RaTG13) and SARS-CoV-2 [10]. Apart from bats, the SARS-CoV-2 genome also has similarities with Pangolin-CoV, namely the coronavirus in pangolins. The S1 protein in SARS-CoV-2 is near its conjunction with Pangolin-CoV rather than coronavirus that infects bat. From this, the initial suspicion emerged that wild animals, especially bats, were the main reservoir for SARS-CoV-2 [11,12].

2.1. Virus Component

The virus's body's structural protein is the central part that helps the host's infection process. There are four main structural components of proteins in coronavirus, including the (Figure 1). Spike protein (S) plays a role in binding mediation, determining the host target, tissue tropism, and the host immune response's primary inductor. Protein Membrane (M) plays a vital role in the morphology of coronavirus. Protein Envelope (E) functions to assemble the virus life cycle, release viruses, and pathogenesis while in the host body. Meanwhile, the nucleocapsid (N) protein has functions in forming ribo-nucleocapsid with RNA (Ribo Nucleic Acid), replication, transcription, and viral translation [13,14].

All Coronavirus types contain specific genes named ORF1. This gene encoded proteins to facilitate virus

replicates the form of nucleocapsid and spike proteins. However, SARS-CoV-2 is a Coronavirus class with a higher transmission rate than other Coronavirus types. SARS-CoV-2 has a receptor-binding domain (RBD) on S protein with more variations than SARS-CoV has. The SARS-CoV-2 protein affinity with ACE2 (Angiotensin Converting Enzyme) as the host receptor was 10-20 times higher than the SARS-CoV protein affinity with the host receptor. Both of these things make SARS-CoV-2 easier to infect the host body than other Coronavirus types [15–17].

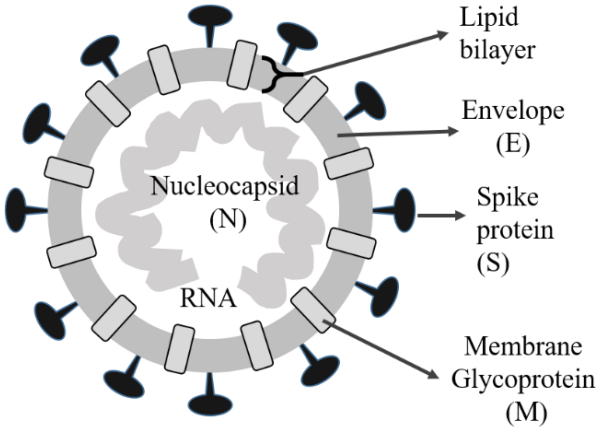

Fig. 1 Schematic diagram of SARS-CoV-2 (Modified from [13,14])

The respiratory tract is the SARS-CoV-2 route entry most concerned about even though this virus can enter the human body inadequately through other routes such as fecal-oral. SARS-CoV-2 initiates infection in the host by attaching viral S protein to the ACE2 receptor. After successful binding, the viral S protein conformation changes to facilitate cell membrane fusion through the endosome pathway. When the membrane fusion is successful, the virus releases RNA in the infected host cell. The viral RNA genome will be translated into two polyproteins and a structural protein by viral proteinases. Viral proteins and newly formed RNA genomes assembled into virions in the endoplasmic reticulum and Golgi cells. The following process is transport through vesicles and the release of new viruses from the cell [12,18].

ACE2, TMPRSS2 (Transmembrane serine protease 2), CTSB (Cathepsin B), and CTSL (Cathepsin L) have a vital role in the process of SARS-CoV-2 infection in the host body (Figure 2). ACE2 plays a role in the binding of the virus to host cells [19]. TMPRSS2 is required to prime protein S to cellular proteases [19,20]. CTSB and CTSL play a role in virus entry in the host body even though they have a less dominant position.

2.2. Cathepsin L (CTSL) Cleavage of the SARS-CoV-2 Spike Protein

Most human organs are susceptible to SARS-CoV-2 infection because ACE2, TMPRSS2, and CTSB / L are present in all human tissues. However, ACE2, TMPRSS2, and CTSB / L replication were found in the heart, kidney, respiratory tract, and digestive tract. An increase in ACE2, TMPRSS2, and CTSB / L in target cells indicates a higher virus risk level [21].

2.3. Human Susceptibility

The most common symptoms felt by someone after being infected with SARS-CoV-2 are fever, dry cough, fatigue, myalgia, and dyspnea. Several other symptoms can also arise, including headaches, prolonged dizziness, abdominal pain, diarrhea, nausea, and vomiting [22,23]. Patients with diabetes, obesity, hypertension, respiratory infections, or cardiovascular occur an overactivation of pro-inflammatory ACE / ANGII / AT1R (Angiotensin II Receptor Type 1) cells, triggering excessive ACE2 replication higher risk of SARS-CoV-2 infection when compared to non-comorbid patients [24]. SARS-CoV-2 infection in comorbid people carries a higher risk of death. Comorbidities themselves have increased the risk of death in a person and will improve many times if there is a COVID-19 infection [25].

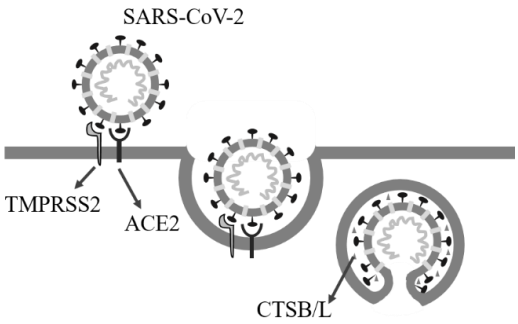

Fig. 2 ACE2, TMPRSS2, CTSB, CTSL and SARS-CoV-2 (Modified from [21])

Comorbid in patients such as cancer cause immunosuppression systemic, excess cytokines, induction of pro-inflammation agents, and impaired dendritic cell maturation due to treatments such as chemotherapy, make it easier for the body to be susceptible to SARS-CoV-2 infection [26–28]. Condition of the decreased immune system also occurs in patients with cirrhosis comorbid. The risk of people with autoimmune comorbidities, such as HIV (Human Immunodeficiency Virus), did not correlate with the higher transmission of SARS-CoV-2 if PLWHA (People Living with HIV/AIDS) had reasonable disease control and self-protection [29].

Comorbidities often found in patients are hypertension, diabetes, and heart disease [23]. Broman et al., in their research, showed that ICU (Intensive Care Unit) patients experience worse health conditions than non-ICU patients. Most of the patients in the ICU ward are patients with comorbid such as obesity. The oxygen saturation in non-ICU patients was higher than in ICU patients at 95% compared to 88%. All patients

with a duration of 20 days after admission to the ICU required invasive ventilation assistance to breathe [30].

Apart from comorbidities, other risk factors that affect the severity of SARS-CoV-2 infection are age and smoking habits. Wang et al. stated that patients in the ICU mainly were patients over 56 years of age [23]. SARS-CoV-2 was found to be more susceptible to infecting males than females [31]. This matter may be associated with higher smoking rates in males than females. Smoking habits can increase the expression of ACE2 receptors, making it easier for viruses to enter the body. This condition is similar to that experienced by comorbid patients [32].

Women with pregnancies did not show a higher severity of SARS-CoV-2 infection than non-pregnant women. Chen et al., in their research on nine pregnant women with SARS-CoV-2 disease, shows that symptoms for all pregnant women have similarity with a COVID-19 general sign such as fever (seven of nine patients), cough (four of nine patients), myalgia (three of nine patients). There was an increase in the aminotransferase concentration in three patients. However, none of the patients showed severity or even died. The study also did not find the vertical transmission of COVID 19 from mother to baby [33].

Patients in the suspect category (asymptomatic or starting to show mild symptoms) are recommended by WHO to carry out molecular examinations to diagnose COVID-19. The method used to detect SARS-CoV-2 is nucleic acid amplification by real-time reverse transcription-polymerase chain reaction (rRT-PCR) and sequencing. The examination specimens are taken from the upper airway (nasopharyngeal or oropharyngeal swab) or samples from the lower airways (sputum, bronchoalveolar lavage (BAL), or endotracheal aspirate) [34]. Although viruses are found in other test specimens, the human body's detection has used chiefly upper and lower airway specimens. Research conducted by Wang et al. stated that the virus was easier to find in bronchoalveolar lavage fluid specimens, sputum, nasal swabs, fiber bronchoscope brush biopsy, pharyngeal swabs, feces, and blood. While the examination using a urine specimen, no virus was found at all [35].

2.4. Virus Mutation

There are currently new challenges worldwide, not only the quick transmission of SARS-CoV-2 but also viral mutations. A new mutation of SARS-CoV-3 was recently discovered, which is more virulent and dangerous than the previous virus. A new virus strain has been infected in China (D.6.1.4.G) and the U.K., called the B.1.1.7 virus. The B.1.1.7 virus showed a higher transmission potential than SARS-CoV-2 [36,37]. The emergence of a new strain of SARS-CoV-2 was also found in South Africa, then dubbed B.1.106. Apart from these two countries, the mutation of the SARS-CoV-2 virus into the B 1.1.28 virus was found, which infected Brazilians. Some mutations that occurred in the new strain of SARS-CoV-2 resulted in faster transmission of the virus. The transmission speed occurs due to gene mutations from previous variants in several virus spike protein regions, making it more aggressive when it binds to the ACE2 receptor [38].

Table 1 Mutation of COVID-19

Mutation	Country	Type of Mutation	Effect of Mutation
D.6.1.4.G [42]	China	Spike protein	Higher transmission potential than SARS-CoV-2
B.1.1.7 [37]	The U.K.	Spike protein	Increases ACE2 binding on hosts
B.1.160 [38]	South Africa	Spike protein	The effect of virus mutations on the host has not been determined
R203K [41]	Australia	Nucleocapsid	Increased virulence and reproduction of SARS-COV-2
B 1.1.28 [43]	Brazil	Spike protein	Acceleration of spike protein replication

2.5. Diagnosis of COVID-19

The diagnosis of COVID-19 is carried out based on the output of the results of the RRT-PCR examination. The RRT-PCR test using nasopharyngeal or oropharyngeal swab samples obtained a cycle threshold value (Ct-value). Ct-value is defined as the minimum amount formed in the amplification process by calculating the fluorescent signal's ability to reach a threshold value. The threshold value used is the Ct-value, which will be inversely proportional to the viral load value, where the lower the Ct-value, the higher the viral load value. A person considered positive COVID-19 if the Ct-value is ≤ 40 [39]. Kleiboeker et al. showed that the range of Ct-values in positive RT-PCR samples ranged from 6.16 to 37.92 [40]. Infection detection of the new SARS-CoV-2 strain is still being carried out using RRT-PCR until now. The examination of the new SARS-CoV-2 strain in the patient's body using RRT-PCR showed a positive result and a high viral load. [37].

2.6. Mutation and Susceptibility

The new SARS-CoV-2 strain had an impact on the virulence level of the virus. In D.6.1.4.G strain, there was a change in the spike protein sequence, increasing virus spike proteins' ability to enter host cells that express a lot of ACE2. Not many different from D.6.1.4.G, B.1.1.7 also changes the spike protein sequence that causing increasing in the ability to bind ACE2 in the host body. In contrast to the B.1.1.60 strain, although it has almost the same protein sequence as D.6.1.4.G, its virulence level has not been identified. However, it is estimated that not many are different with D.6.1.4.G. While, R203K is a new strain of SARS-CoV-2 that undergoes changes in the nucleocapsid and increases in the ability of the virus to

reproduce in the body host. The new strains that recently emerged in Brazil occur, accelerating the spike protein replication, resulting in virus replication, and accelerating virus proliferation in the host body [37,41–43].

The viral load of SARS-COV-2 did not correlate with the severity of the patient's condition because there was no difference in viral load values in patients with mild and severe infections [39]. Viral load values were also unrelated to patient ward rooms, duration of invasive ventilation support for breathing, and patient survival [44]. In all cases, the viral load value peaked at the beginning of SARS-CoV-2 infecting the human body, namely 0.7 days before asymptomatic symptoms appeared, so it is necessary to increase awareness of the virus's transmission at the time of infection. Viral load values can be used as a basis for determining epidemiological measures to track the likelihood of another person being infected with the virus [45, 46].

3. Results and Discussion

D.6.1.4.G is the SARS-CoV-2 virus mutation identified in China and thought to be the critical mutation that causes high transmission worldwide. D.6.1.4.G and R203K are thought to be related to the severity of the patient's disease because they were found to be in a patient with severe disease and require intensive care in an inpatient ward. However, further research is still needed to detect the infection of the new SARS-CoV-2 strain on disease severity. B.1.1.7 is a SARS-CoV-2 mutation in the United Kingdom with a higher transmission rate than other viral mutations and SARS-CoV-2 itself. Meanwhile, strain B.1.1.28 is a new strain of SARS-CoV-2, identified when Japanese tourists got sick after visiting Brazil. B.1.1.28 was found to be no more infectious than the SARS-CoV-2, and the rate of spread tended to be constant. Unlike the B.1.106 strain, which infects many health workers, the impact of infection from the virus has not been known until now [37, 41–43].

4. Conclusion

The COVID-19 pandemic is a world health problem that has not been resolved until now. The continuation of the pandemic started from the ease of human-to-human transmission. SARS-CoV-2 as a transmission agent is included in the beta coronavirus group and classified in the same family as SARS-CoV and MERS-CoV, which caused the outbreak in the previous year.

There are four main structural components of proteins in coronavirus, including the Spike protein (S), Membrane (M), Envelope (E), and Nucleocapsid (N), each of which functions to assist virus transmission to the host body and viral pathogenesis. Virus transmission to the host body begins with the binding of the viral S protein with ACE2. The transmission process continues until the virus succeeds in infecting cells and replicating them in the body. Frequent direct contact and droplet splashing can facilitate the virus's transmission body, even though there are other inadequate proportions routes. Although everyone can be infected, the risk factors for transmitting the virus can be more significant in people with comorbidities. Symptoms of a viral infection can differ from one person to another. The new mutations of SARS-CoV-2 have been found more virulent and dangerous in several countries around the world. The rRT-PCR examination is needed to diagnosis a patient with COVID-19. RRT-PCR result is defined as Ct-value; this is a minimum amount formed in the amplification process.

There is a potential relationship between viral virulence and host susceptibility. Viral mutations influenced the virulence of the SARS-COV-2 virus. We hope that this study can be used as a basis for further research on viral mutations and their impact on host susceptibility. The clinical implication of the SARS-CoV-2 transformation is that the beta coronavirus is easier to infect a person. Patients have the opportunity to be newly infected or reinfected with the mutated SARS-CoV-2 virus and even reinfection in someone who has been vaccinated against COVID-19. Reinfection cases can be the same or more severe than the first COVID-19 infection. Genome sequencing examination of SARS-CoV-2 needs to be done both in cases of new infection and reinfection if facilities are available. The limitation of this study does not explain the viral mutation process that infects the host and does not explain the cause of mutation. The SARS-CoV-2 mutation is likely to be more common and may make it easier to infect humans in the future.

Further research is needed to explain the process of viral mutation and the virulence levels associated with the new mutation. Patient susceptibility was influenced by levels of ACE2, TMPRSS2, CTSB, and CTSL. Examining the type of mutation and the relationship of exposure to a person needs to be investigated further. Vulnerability also needs to be analyzed based on comorbidities that can worsen the severity of COVID-19. Viral mutations may be associated with increased susceptibility to someone infected with COVID-19.

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