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SPECIAL ISSUE

MOLECULAR REVIEW COVID19 FROM THE PATHOGENESIS AND TRANSMISSION ASPECT

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Abstract

Introduction: Corona virus disease 2019 (COVID-19) spread and caused a pandemic that affected people all over the world. COVID-19 is also called Severe Acute Respiratory Syndrome-Coronavirus Disease (SARS-CoV). ***Discussion:*** *COVID-19 is a β-coronavirus serotype which is a single strain of RNA virus and was an outbreak in 2002 (SARS-CoV) and 2012 (MERS-CoV). COVID-19 has Open Reading Frames (ORFs) consisting of Spikes (S), Envelopes (E), Membranes (M), and Nucleocapsids (N) with S parts being a glycoprotein that can attach to receptors owned by host cells, the receptors are CD 26, ACE-2, Ezrin, and Cyclophilins with the main receptor being ACE-2 in the lung organs. Process would evoke a host body's immune response consisting of natural and adaptive immune systems, involving the Antigen Presenting Cell (APC) system which consists of two, namely: Major Histocompatibility Complex (MHC) class I and II. APC could also generate adaptive immune system, consists of B and T cells. COVID-19 had the ability to survive in B and T cells, so that cytokine-chemokine secretion continues to be known as cytokine storm that trigger Acute Respiratory Distress Syndrome (ARDS) and death.* ***Conclusion:*** *The recovery prognosis of COVID-19 depended on the detection of COVID-19 patients because it was related to the severity of ARDS, so the earlier it was detected, the greater the chance of recovery.*

Topics 8. Airborne Aerosol Distribution and Coronavirus Transmission

INTRODUCTION

New Years's Eve 2020, that was celebrated on December 31st, 2019, might be a New Year's Eve that would not be forgotten by all residents living in the city of Wuhan, Hubei, in Republic of China. Wuhan is a wet seafood market that sells various types of animals such as raccoon bats, snakes, ferrest, and other types of animals. At that time, a new outbreak of disease was reported known as *novel Corona Virus-19* (nCoV-19), trigerring cases of pneumonia that had never been encountered before (1-4).

In Indonesia, data on 28 June 2020 reported 51.427 confirmed cases (increased by 1,240 cases), 21,333 recovered and 2,683 deaths (increased by 63 deaths), putting Indonesia as the number one country with the highest number of cases in the Southeast Asian Regions. Five locations with the most SARS-CoV-2 infections in Indonesia are: East Java (10,901 confirmed cases, 3,429 recovered, and 796 deaths), Jakarta (10,796 confirmed cases, 5,542 recovered, 616 deaths), South Sulawesi (4,469 confirmed cases, 1,617 recovered, and 157 deaths), Central Java (3,097 confirmed cases, 1,030 recovered, and 150 deaths), and West Java (3,014 confirmed cases, 1,489 recovered, and 175 deaths). SARS-CoV-2 infection may cause death which is exacerbated by preexisting chronic comorbid diseases (heart disease, cerebrovascular disease, Diabetes Mellitus, cancer, and the other chronic diseases) (5).

The exact agent of zoonotic infection has not been confirmed but bats are thought to be the main reservoir because SARS-CoV glycoprotein DNA recombination (CoVZXC21 or CoVZXC45) and *Receptor Binding Domain* (RBD) were found in bats. Covid19 is also referred to as *Pneumonia Associated Respiratory Syndrome* (PARS) and because of the similarities with *Severe Acute Respiratory Syndrome-Corona Virus* (SARS-CoV) infection that once spread in 2003, Covid19 is also known as *Severe Acute Respiratory Syndrome Corona Virus 2* (SARS-CoV-2) (6).

Identification, based on the results of laboratory analysis, found that the pandemic was caused by corona virus, therefore WHO named this disease as Covid19. The corona virus genome, extracted from Covid19 patient in Wuhan, reveals that it consists of 30,000 base pairs which is translated into a corona virus protein after infecting host' cells. Gene sequence 5'-replicase ORF1ab-envelope (E)-membrane (M)-N-3' (4-5).

Covid19 pandemic in 151 countries was not the first infection by corona virus, because there have been two infections caused by corona virus: SARS in 2003 which occured in Guangdong China, and around 2013 corona virus became widespread again in Middle East area, which was named as Middle East Respiratory Syndrome Corona Virus (MERS-CoV). The differences among these diseases were described in table 1 (7-9).

The main difference among SARS-CoV, MERS CoV, and SARS-CoV-2 is in its transmission capability. SARS-CoV in 2003 infected 8,098 people with a transmission rate of 9% among 26 countries in the world with a mortality rate of 9.6%, MERS-CoV infected 2,428 people, while SARS-CoV-2 infected 120,000 people with a transmission rate of 2.9% and mortality rate of 3.61%. The transmission capability of SARS-CoV-2 is higher than SARS-CoV and MERS-CoV because of its genetic recombination in S protein in its binding region with ACE-2, thereby increasing its transmission capability (10).

Table 1. The Different Between SARS-CoV-1, MERS-CoV, and SARS-CoV-2

Category	SARS-CoV 1	MERS-CoV	SARS-CoV-2
Human Receptor	Angiotensin Converting Enzyme -2 (ACE-2)	Dipeptidyl Peptidase-4 (DPP-4)/Cluster of Differentiation 26 (CD 26)	Angiotensin Converting Enzyme-2 (ACE-2)
Manifestation	Cough, fever, malaise, difficulty breathing	Pneumonia, respiratory injury	Cough, fever, and difficulty breathing
Main animal reservoir (Zoonosis)	Bat	Bat	Bat
Intermediate animal reservoir (Zoonosis)	Civet	Camel	Pangolin
Disease	Severe Acute Respiratory Syndrome (SARS), Acute Lungs Injury (ALI), Acute Respiratory Distress Syndrome (ARDS)	Middle East Respiratory Syndrome (MERS)	Severe Acute Respiratory Distress Syndrome 2 (SARS 2), Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), Coronavirus Disease-19 (COVID-19)
Fatality rate based on sex	Men had higher fatality rate	Men had higher fatality rate	Men = 4.75% compared to women = 2.75%
Place of pandemic	Guangdong, China	Arab Saudi	Wuhan, Hubei China
Year of pandemic	2003	2013	2019
Estimation of suffering people	8,098	2,428	123.882
Mortalitas	776 (9.6%)	838	4473 (3.61%)
Transmission	9% of 26 countries	-	2.9% dari 109 countries

The similarity among these three viruses are all of the infections caused by β-corona virus with symptoms of pneumonia, followed by Acute Lung Injury (ALI), Acute respiratory Distres Syndrome (ARDS), and might cause death. Animals that play roles in SARS-CoV, MERS-
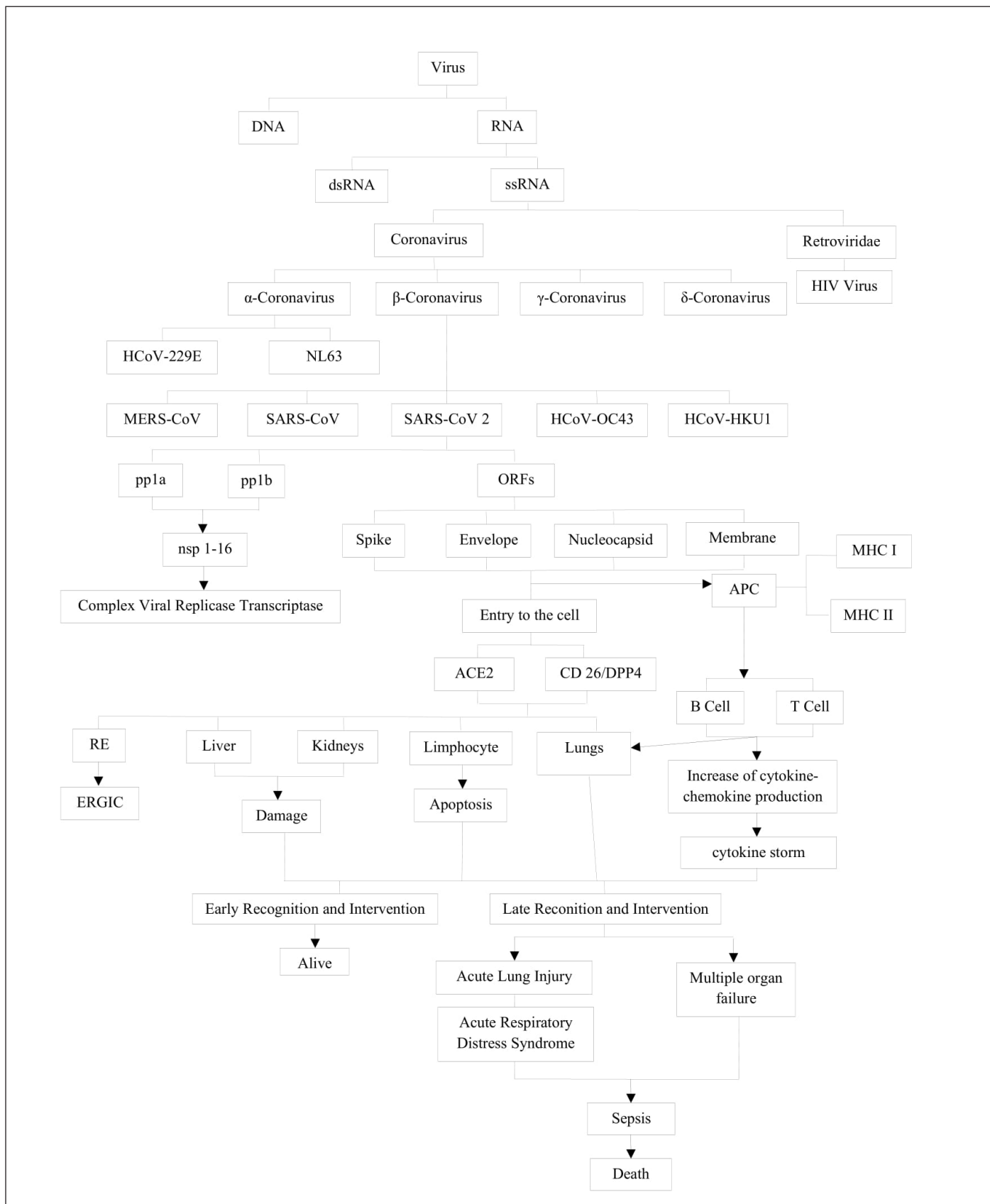
Figure 1. Pathogenesis conceptual framework of COVID-19 (1,15,28,49)

CoV, and SARS-CoV-2 zoonotic infection consist of two types of animals, main and intermediate reservoir. The main reservoir animals are bats, while their internediate reservoir animals are civets (ferret species), camels, and pangolins (pangolins species), respectively (10-12).

DISCUSSION

Corona Virus Disease - 19 (Covid19)

SARS-CoV-2 is similar to previous diseases that were epidemic in 2003 and 2013. Based on the relationship between previous viruses with SARS-CoV-2,

the similarity level between SARS-CoV-2 with SARS-CoV is 88%, and the similarity rate with MERS-CoV is 50%, therefore SARS-CoV-2 or Covid19 or PARS is a form of mutation of both the SARS-CoV and MERS CoV viruses described in Figure 1. This is based on the fact that SARS-CoV-2 is a member of the Corona virus family which is a group of RNA viruses (β coronavirus) with a particle size of 120-160 nm and divided into several types: α, β, γ and δ Co-V (18,20).

Covid19 infection is included in zoonotic infections that is transmitted from main and intermediate reservoir animals, which are bats (Horseshoe Bat species or Rhinolopus sinicus) and pangolin. Coronaviruses are infectious in several mammal species (α and β CoV) and also avian/bird species (γ and δ CoV). Coronavirus attacks the upper respiratory tract in humans, which are the α-CoV, HCoV 229E, HCoV NL 63, β-CoV, HCoV-HKU1, and HCoV OC 43 types, with symptoms that are similar to common flu diseases (3,13-15). The incidence of this infection is mostly found in male patient age 34-59 years. The incidence of this infection is also exacerbated by chronic comorbid diseases (heart disease, cerebrovascular disease, and diabetes). The highest proportion of cases is in elderly age 60 years above with concomitant comorbidities. Incidence in children under 15 years old is very rare (16).

SARS-CoV is a group of single stranded RNA viruses (ssRNA), meaning that there is only RNA in its genetic material content. RNA virus class is a group of virus that is easily mutated. Judging from its differences with SARS-CoV virus, SARS-CoV-2 virus has the similar hijacking site, which is ACE-2. This hijacking site is related to ribosome, which is the site of protein synthesis through transcription-translational stage. This is the initial base of SARS-CoV-2 transmission process, both in sick individuals and in corpses that are corona virus positive to the surrounding environment. Corona virus must attach to host cells, because without attaching to its host cells, it is only an inanimate object. Corona virus can also be called obligate parasite (19-20).

Covid19 level on several materials

SARS-CoV-2 might reside in an object surface before it enters a host's body. This is represented by *Tissue-Culture Infectious Disease* (TCID$_{50}$) per millimeter on several types of materials, which are: air (aerosol), plastic, aluminium (stainless steel), copper, and cardboard, which are shown in table 2. SARS-CoV-2 virus is more stable on plastic and aluminium (stainless steel) compared to copper and cardboard with an ability to last up to 72 hours. The SARS-CoV-2 virus TCID$_{50}$ titer on plastic and aluminium decreases from $10^{3.7}$ to

$10^{0.6}$ per millimeter in 72 hours after exposure on plastic and similar result is found on aluminium surface after 48 hours, whereas on copper particles and cardboard there was no TIDC$_{50}$ SARS-CoV-2 virus 4 to 8 hours after exposure. In addition, SARS-CoV-2 and SARS-CoV 1 viruses were similar in aerosols, with a median of about 1,1 to 1,2 hours and credible interval 95% from 0.64 to 2.64 for SARS-CoV-2 and 0.78 to 2.43 for SARS-CoV-1 (15).

Table 2. Level TCID$_{50}$ Covid19 on Materials

Material	Level of TCID$_{50}$	Time
Plastic	$10^{3.7}$-$10^{0.6}$	72 hours
Aluminium	$10^{3.7}$-$10^{0.6}$	48 hours
Copper	0	4-8 hours
Cardboard	0	4-8 hours
Aerosol	0.64 - 2.64	1.1-1.2 hours

SARS-CoV-2 virus spread in the air is more likely to be caused by droplets that are released by symptomatic patients, which come from a person's cough or sneeze. The number of droplets that are released from coughing is 3.000 droplets and might survive in the air, especially its transmission is more vulnerable in public toilet. There are three kinds of droplet, such as: large infectious droplets, small infectious droplets, and infectious droplet nuclei. The differences among them are large infectious droplets quickly fall to the ground after traveling up to 1 until 3 feets, it is still encased with mucus or water, and viruses inside the large infectious droplets are aerosolized by the infector or toilet water. Small infectious droplets fall to the ground after traveling 3 until 5 feets, it can become droplet nuclei because of mucus or water coating the droplets starts to evaporate (18).

Infectious droplet nuclei is the droplet that has size below 5 microns and it can float in the air for prolonged periods because of its microscopic size. Droplet transmission is different from airborne transmission. Droplet transmission occurs when bacteria or viruses travel on relatively large respiratory droplets (such as droplets come from sneezing, coughing, and exhaling). It can only travel on short distances (usually less than 2 meters). Different from droplet transmission, airbone transmission occurs when bacteria or viruses travel in droplet nuclei that become aerosolized, so that healthy people can inhale this droplet into their lungs (19).

These types of transmission can be met both on dentistry and medical practice, so that it can be crosslink transmission between the dentists and general practitioners to their patients. SARS-CoV-2 lasts longer on stainless steel and plastic surface in experimental

setting with estimated half-life median is about 5.6 hours on stainless steel and 6.8 hours on plastic. These materials might be found around individuals (healthy or sick), and are called Building Environments (BEs). BEs consist of a biotic and abiotic environment that might be potential in virus spreading, infection, and transmission process between healthy and sick individuals, where sick individuals and their surrounding environment has the most frequent frequency in health facilities (17,19).

Table 3. Point of Transmission Viruses SARS-CoV-2

Point Conctact	Transmission Process
Milk bottle or daily morning newspaper	Milkman or paperboy
Elevator/Escalator buttons	People and patients under supervision or asymptomatic people who touch the buttons
Handles in public facilities and transportations	People and patients under supervision or asymptomatic people who touch the handles
Door bell	People and patients under supervision or asymptomatic people who touch the door bll
Fruits/vegetables that are sold at the market	People and patients under supervision or asymptomatic people who touch the displayed fruits/vegetables
Shopping bag at the market	People and patients under supervision or asymptomatic people who touch the shopping bag
Cafetaria	People and patients under supervision or asymptomatic people who visited the crowd at the cafetaria
Public toilet	People and patients under supervision or asymptomatic people who used the toilet
Note/bill	People and patients under supervision or asymptomatic people who touch the note/bill
Clothes	Clothes that ar worn by people and patients under supervision or asymptomatic people
Door knob/handle	People and patients under supervision or asymptomatic people who touch the door knob/handle

Contact points of SARS-CoV-2 virus transmission might occur due to contact with objects shown in table 3. They are closely related to the concept of transmission and spread of virus from one person to another through its connection with public facilities. To minimize SARS-CoV-2 virus transmission process after touching materials mentioned in table 3, it is highly recommended to wash hands immediately and use a hand sanitizer. SARS-CoV-2 virus might remain on the object surfaces in table 3 within 24 to 48 hours (12).

Corpses that are SARS-CoV-2 positive might also infect and transmit the virus to their surroundings. World Health Organization (WHO) suggests that funeral processions for confirmed patients must be carried out in no more than four hours. During this time, body cells in the body have not undergone necrosis, so the possibility of SARS-CoV-2 virus transmission is not occurred yet, but the patient's body still has to be wrapped in plastic according to WHO protocol standards and buried in a cemetery far from water sources and residents based on WHO regulation for burial and disposal of Covid19-related waste. This protocol is carried out to prevent SARS-CoV-2 virus transmission from corpses to their surrounding environment, because the body might excrete droplets (20-22).

Autopsy process, that is carried out on a confirmed patient, must be done with extra precaution in transmission-susceptible area of the body, which are respiratory organs (proximal and distal parts of trache, right and left bronchus, and right and left lung), liver, kidney, heart, spleen, and gastrointestinal tract organs. The autopsy process is recommended 12 hours after death and conducted in a high level of biosafety room using Aerosol-generating procedures (AGPs) protocol. Corpse storage is carried out in temperatures ranging from 4-8°C and people (as minimum as possible) in charge of the autopsy are recommended to use a specific mask that can provide protection against respiratory organs, mainly by using an N95 mask, and use a triple-layered mask. Autopsy process starts from the abdomen, pelvic area, and the neck, followed by the chest, and the last part is cranium area (23).

To minimize contamination process, autopsy was performed in an autopsy bag, and after the autopsy process all used equipments were decontaminated using 0.5% iodine solution for three minutes and mucous membrane of the body was washed with 0.05% iodine fluid. Material specimens collected during the autopsy process are collected and fixated in formaldehyde solution, and carefully wrapped using two types of containers with second-layered container could be wrapped in plastic bags made of non-absorbent material. These waste products might be in the form of Personal Protective Equipment (PPE) that is used by health workers in treating confirmed patients both alive or dead. Waste products from isolation unit used to treat patients with Covid19 are also included because according to WHO, Covid19 is suspected to be transmitted through waste products of Covid19 patients (in the form of feces, stool, urine) in bathrooms (21,20).

Virus transmission process is reflected by Reproductive Number 0 (Ro) and Case Fatality Rate (CFR) values. The formula for calculating CFR value is the total number of deaths divided by total number of positive cases multiplied by 100. The CFR value for each of SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses is 11%, 25-43%, and 1-42%. Ro is a value that reflects an SARS-CoV-2 virus infected individual chance to transmit the virus to a susceptible group of people, where Ro value for SARS-CoV-2 is 2-3.5. A SARS-CoV-2 Ro value that varies from 2-3.5 means that one infected person

(whether in a crowd in the form of a party, gathering, or in public place and transportation) has the potential to transmit 2-3.5 people around him without practicing physical distancing. The graph of Ro transmission rate values will be shown in figure 2 (12,16).

Three types of values that are used to interpret Ro values, which are: Ro value smaller (<) than 1, which means that infection will disappear over time and the potential for transmission is very small or almost none. Ro value equal to (=) 1, which means that the infection will be endemic and persist in certain populations. Ro value greater than (>) 1, which means that there will be a high level epidemic and the potential for transmission to others is high with number of outbreaks that will continue to increas. Based on Ro value interpretation, SARS-CoV-2 virus has Ro value ranging from 2 to 3,5, which means that SARS-CoV-2 virus epidemic is occuring and the potential for transmission to others is very high with the number of outbreaks that will continue to increase (23-24).
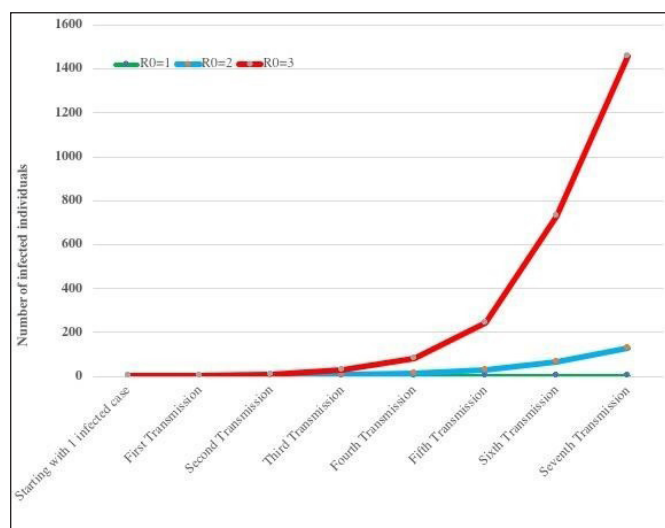

Figure 2. Dynamic Graph Representation of the Spread of SARS-Cov-2 Virus Infection in Populations Based on Ro Values (13)

Figure 2 explains the dynamic graph of SARS-CoV-2 virus infection spread in infected population to population. The X-axis shows the number of times the transmission starts in infected people from first to seventh, while the Y axis shows the number of individuals that will be infected based on Ro values starting from Ro value = 1 (marked with a green line), Ro = 2 (marked with a blue line), and Ro = 3 (marked with an orange line) (12).

Molecular Aspect Review of Covid19 Pathogenesis

Corona virus has four main structures: N protein (Nucleocapsid), M glycoprotein (membrane), S glycoprotein (spike), and E protein (sheath) shown in figure 2. All of major structures are coded in 3 end of the viral genome and included in Open Reading Frames 1a

/ 1b (ORFs-1a / 1b). ORFs-1a / 1b are owned by two-thirds of RNA viruses, including SARS-CoV-2. S protein (150 kDa), utilizing N-terminal signal sequences to gain access to ER. Homotrimer viruses are coded by S proteins to form a distinct protrusion structure on the virus surface. Trimeric glycoprotein is a class I fusion protein and mediates attachment to host receptor. S protein is divided by proteases into two polypeptides (S1 and S2) with S1 forming a large receptor binding domain and S2 forming a protuberant molecular shaft (14,18).

M protein is the most abundant structural protein in virion, consisting of 3 transmembrane domains. M protein has a small N-terminal glycosylation ectodomain and a much larger C-terminal endodomain that extends 6-8 nm into virus particles. M protein does not contain a signal sequence even though it is co-translated into ER membrane. Recent studies have shown that M protein exists as a dimer in virions and adopts two different forms of conformation to increase membrane curvature and nucleocapsid binding ability. E protein (8-12 kDa) is found in small quantities in virions transmembrane protein as its membrane topology. E protein has terminal-N ectodomain and terminal-C endodomain and has ion channel activities and facilitates assembly and release of viruses (14,18,24-25).

N protein is the only protein present in nucleocapsid which consists of two separate domains N-terminal domain (NTD) and C-terminal domain (CTD). Both domains are able to bind RNA in vitro, but each domain uses a different mechanism to bind RNA. N protein is highly phosphorylated to trigger structural changes that increase the affinity of viral versus non-viral RNA. Two specific RNA substrates have been identified for N protein; TRS and genome packaging signal. Genomic packaging signals have been found to bind specifically to second C-terminal RNA binding domain (26).

N protein also binds to NSP1, NSP2, NSP3, NSP4, NSP5, NSP6, NSP7, NSP8, NSP 9, NSP10, NSP12, NSP13, NSP13, NSP 14, NSP 15, and NSP 16. NSP 1 plays a role in virions assembly inside host cells at slower pace, thus preventing the assembly of an antiviral immune system that can inhibit virions assembly. NSP 2 plays a role in the process of endosomes production around host cells. NSP3 has two important tasks for corona virus: releasing other viral proteins, inducing the protein to do its own task, and altering many of proteins from the infected cells. NSP 4, alongside NSP 3 and NSP6, form bubbles inside infected cells (26).

The contents of these bubbles are new assemblies of virion particles. NSP 5 is a protein that functions like a "scissors" to activate other NSP proteins in accordance with their function. NSP 7 and NSP 8 help

NSP 12 to make new RNA genomes inside new virus particles. NSP 9 infiltrates small channels in infected cells nucleus, thus playing a role in molecule movement in and out of the nucleus. NSP 10 and NSP 16 act as genetic camouflage with their main objective are to trick the antiviral that is produced by host cells. NSP 12 plays a role in viral genome genetic letters assembly. NSP 13 unlocks the host cell protein and is associated with production of new virus particles copy. NSP 14 functions as an error-cutting protein due to the synthesis of new virus particles by NSP 12. NSP 15 functions in the process of camouflage from host cell defenses detection against virus-infected host cells (26).

Healthy cells will generally produce expression marks to induce apoptosis, but corona virus' NSP3 and NSP16 might remove this expression marks (camouflage), therefore altering protein balance and reduces the cell's ability to fight viruses. Protein interaction helps tether the viral genome to replicase-transcriptase complex (RTC), and package the encapsulated genome into virus particles. The fifth structural protein, hemagglutinin-esterase (HE), acts as hemagglutinin which function is to bind sialic acid on glycoproteins surface and contain acetyl esterase activity. HE increases cell entry mediated by S protein and spread of the virus through mucosa (26-27).

Coronavirus virulence into host cells starts from attachment and invasion process of Covid19 virus particles into mucosa, where S1 protein played its role, into receptors that match S1 protein, which are: Angiotensin Converting Enzyme-2 (ACE-2) (12). ACE-2 can be found in the entire body mucosa, which plays the most important role in respiratory tract especially the upper part of the lung where the virus hijacking. S1 protein only attaches ACE-2 receptors that are present in respiratory cells, alveolar epithelial cells, vascular endothelial cells, and macrophages (16-17). In addition to location factors, other factors that influence virulence of S1 to ACE-2 are cathepsin A / B, TMPRSS2 as well as its compatibility with Receptor binding Domain (RBD), Receptor Binding Motif (RBM), and Transmembrane Domain (TD) between Spike S1 with ACE-2. Inhibition of factors that affect virulence of S1 to ACE-2 will not cause S1 to attach ACE-2 even though ACE-2 is a receptor of S1 corona virus. (28-29)

After the bond between S1 and ACE-2 is matched, S2 spike plays a role in entering with its main target being rough Endoplasmic Reticulum (RE) of host cell, because in rough RE ribosomes can be found and needed to conduct transcription-translation process. This is consistent with the central dogma theory that links the process of protein transcription-translation by DNA through ribosome material on rough RE. When S2 spike enters the host body, there is resistance from host cell through recognition by various molecules that act as Antigen Presenting Cells (APCs), such as macrophage cells, NK cells, Dendritic Cells (DCs) and other cells that act as Major Histocompatibility Complex I and Major Histocompatibility Complex II (MHC class I and II) and Human Leukocyte Antigen I and II (HLA I and HLA II) with HLA associated with SARS-CoV disease (consisting of HLA-B * 4601, HLAB * 0703, HLA-DR B1 * 1202, and HLA Cw * 0801) and HLA that function for protection against SARS-CoV (HLA DR 0301, HLA-Cw 1502, HLA-A * 0201). Innate immune system aims to eradicate viral infections from infected cells (10,29-30).

APCs (NK cells, macrophage cells, mannose binding lectins (MBL), and DC cells) in addition to phagocytosis of corona virus particles, also present them to B cells (humoral immune responses) and T cells (cellular immune responses). DC acts as a link between innate immune system and adaptive immune system because it has receptors to recognize antigens, whcih are: Toll Like Receptors (TLRs), c-type lectins, and Pattern Recognition Receptors (PRRs) that recognizes Pathogen Associated Molecular Patterns (PAMPs). TLRs that recognize PAMPs are TLR-3, TLR-7, TLR-8 and TLR-9 can recognize DNA and RNA viruses in endosomes (30).

In addition, RNA virus receptors also induce cytosolic melanoma differentiation-associated gene 5 (MDA-5) receptors and cyclic GMP - AMP nucleotidyltransferase synthase (cGAS) associated with viral RNA and DNA introduction in cytoplasm. The work of two receptors forms an adapter signaling complex consisting of: TIR-domain-containing protein adapter including TNF-β (TRIF), mitochondrial-antiviral signaling protein (MAVS), and stimulator of interferon genes protein (STING) to trigger the formation of a molecular cascade, involving Myeloid differentiation-88 Myd88), resulting in Nuclear Factor Kappa Beta (NF-KB), interferon regulatory factor-3 (IRF-3), αβ interferon, and a number of pro-inflammatory chemokine-cytokines activation. In addition, NF-KB also activates Intracellular Adhesion Molecule-1 (ICAM-1) which eventually increases vascular permeability and facilitates vascular edema (31).

Danger signal from DC will be responded by B cells and T cell, therefore provoking B cells and T cells considering that DC causes polarization of T helper (Th) cells and eventually induces differentiation into Th 1 and Th 2 cells. Th 1 cells are known to originate from CD 4+ cells which then differentiates into Th 1 cells and Granulocyte Macrophage Colony Stimulating Factor

(GM-CSF). In addition to DC presentation, when corona virus enters the cell, PRRs receptor releases viroporin owned by DC which might activate nucleotide-binding domain, leucine-rich-containing-family, pyrin-domain-containing 3 (NLRP3) which is an inflammasome. NLRP 3 activation activates pro Interleukin 1β (pro IL-1β) to become IL-1β (31-32).

B cells system (Humoral Immune Response) will differentiate into plasma cells (producing specific antibodies / Abs against viral antigens / Ag). The formed antibodies act as virus neutralizer and inhibitor from entering the host cell and also act as a protective defense. Humoral immune system plays a role in envelope part of the SARS-CoV-2 virus, specifically in Spike, Nucleocapsids, Membranes, and E protein (viral envelope). B cells will bind to ACE-2 receptor which is attached to SARS-CoV-2 virus. Unlike the humoral immune system, cellular immune system acts as an adaptive immune response and in contrast is found in infected cells mediated by T lymphocyte. T helper cells directly play a role in all adaptive immune systems, whereas cytotoxic T cells play a role in clearing and killing virus-infected cells (10).

DC migration from lymphatic nodular tissue to APC triggers an adaptive immune system to secrete various cytokines-chemokines aimed at destroying the corona virus. Secreted cytokines include: Macrophage Inflammatory Protein 1 α (MIP-1α), Interferon, IL-1β, IFN-γ, IP-10, Monocyte Chemotactic Protein 1 (MCP-1), IL-4, IL-10, Il-Il -2, IL-7, Granulocyte Colony Stimulating Factor (GCSF), and TNF-α. The secreted chemokines consist of: CCL-2, CCL-3, CCL-5, CXCL-8, CXCL-9, and CXCL-10. APC provocation against B cells is a humoral adaptive immune system through increased secretion of immunoglobulin G and M (IgG and IgM) (31-33).

Corona virus has the ability to escape from B cells and T cells and even live inside T cells (especially CD 8+) and might cause damage to lungs. This makes the body's immune system continue to produce cytokines-chemokines, therefore causing excess cytokines-chemokines production that trigger an emergency condition in medicine called sepsis. Excessive production of cytokines-chemokines cause negative effects on respiratory cells in lungs because corona virus attacks the respiratory tract, therefore secretion of cytokine-chemokine is damaging the respiratory tract (alveoli, lungs, and other respiratory organs) (33-34).

Outcome for recovery depends on the disease stage. The faster it is detected, the outcome will be better for recovery and patient might survive. Often infected people are asymptomatic, therefore delaying treatment and causing Acute Lung Injury (ALI), with one form of ALI is Acute Respiratory Distress Syndrome (ARDS), and sepsis. Characteristics of ARDS are pulmonary edema, severe hypoxia, and accumulation of inflammatory cells in lungs that might cause death (35).

Covid19 Diagnosis

Procedure diagnosis for Covid19 based on China National Health Commission was determined from patient's travel history to affected area (within the last 14 days) and supported with several types of laboratory tests: real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, genome sequencing, serological evaluation of anti-viral immunoglobulin (IgG and IgM), and radiological examination of lungs. In SARS-CoV-2 examination process through RT-PCR, samples were obtained from throat, sputum, and lower airway secretions swabs, blood tests, and history of symptoms experienced by Covid19 patients. Symptoms experienced by Covid19 patients generally are: dry cough (80% of cases), anosmia, asthenia, taste dysfunction, myalgia (18% of cases), headache, diarrhea (11% of cases), odynophagia, fever (temperature > 38°C in 86% of cases), anorexia, dyspnea, abdominal pain, vomiting (15% of cases), difficulty for breathing (47%), and conjunctivitis (36-38).

More than half of patients report dysfunction in taste and anosmia, which might be in the form of no symptoms for taste dysfunction or anosmia, anosmia only, or taste dysfunction only. The cause of taste dysfunction and anosmia in patients with Covid19 are still unclear, but there is one possible reason that can be related to taste dysfunction and anosmia. The average period of taste and olfactory dysfunction is 2.8 days ranging from 1 to 4 days and indeed can be one of the disease manifestation that attacks respiratory tract (including SARS-CoV-2 virus). This is related to damage of gustatory and olfactory cells caused by SARS-CoV-2 virus (39).

As previously explained, SARS-CoV-2 virus is attached to ACE-2 receptor. ACE-2 is present in both oral mucosa and olfactory mucosa, therefore damage of both types of mucosa might cause taste and olfactory dysfunction. Taste dysfunction symptoms might come out as total loss of taste, metal taste, bitter taste, salt-like taste, and loss of ability to taste sweetness. Loss of ability related to olfactory organs can be classified as qualitative or quantitative loss and has an impact on life, because the ability to smell affects food selection and nutrition intake, pleasure in food, ability to detect harmful substances associated with toxic and toxic substances, and influences quality of life. Taste and olfactory ablty examination might be used as one of screening

examinations for suspected cases, but this examinations have their limitations (36). These examinations are very subjective and might be influenced by mood, pleasure, and patient anxiety (40-41).

RT-PCR test might be supported by two other tests: blood test and radiological examination of lungs. Additional blood tests in infected patients often might revealed thrombocytopenia (leukocyte counts below 1000) and are often associated with severe stage of disease. Radiological examination of lungs (CT scan of lungs) in confirmed cases generally shows viral infiltration with formation of ground-glass opacity, but might remain normal in initial stage. Slight abnormalities might also be found in the form of thickening in both lungs and accompanied by lymphadenopathy. RT-PCR and serology are often combined with CT scans of lungs, and there is a correlation between the two tests, where commonly lung lesions that are found will give a positive swab result (42-43).

Patients can be grouped into several statuses from the Covid19 examinations. Probable cases has an operational definition as monitored patient (PDP) who has been examined for Covid19 but the results are inconclusive, and are different from confirmed cases. A confirmed case occurs when a positive laboratory examination result Covid19 with all kinds of clinical findings. In addition, the term asymptomatic person (OTG) might also be found, which has an operational definition of people who have no symptoms but are at risk of contracting or having close contact with Covid19 patients. Operational definition of close contact is an individual with direct physical contact without using any means of protection, and being in the same environment (office, class, home, party, etc.) or talking within a 1 meter radius with a PDP, probable (low risk contact) or confirmed patients (high risk contact) within 2 days before symptoms begin until 14 days after symptoms develop (43-47).

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CONCLUSION

Outcome for Covid19 patients is depended on the severity of patient the first time when they seek treatment, the faster it is detected the higher the cure rate is. It is necessary to produce monoclonal antibodies that might inhibit the attachment of S1 proteins to ACE-2 receptors found in host cell body (host), especially in lungs, and materials to reduce TIDC50 virus level in Built Environments (BEs) on aerosol medium, aluminum, and plastic.

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