REVIEW ARTICLE

Acute Respiratory Distress Syndrome (ARDS) as the Main Causative Death in Coronavirus Disease-19 (COVID-19) Patients

Fery Setiawan[1,2], Arif Rahman Nurdianto[3,4,5,] Retno Pudji Rahayu[2*], Heni Puspitasari[5], Eta Radhianto[6]

[1] Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Indonesia
[2] Department of Oral Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3] Lecturers at Anwar Medika University
[4] West Sidoarjo Hospital, Sidoarjo, East Java
[5] Toxoplasma study group, Institute of Tropical Disease, Universitas Airlangga
[6] Dental Research Centre, Faculty of Dental Medicine, Microbiology Division, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

An adequate immune system is needed eliminate of pathogens and infectious diseases. COVID-19 is one of the most contagious respiratory diseases transmitted by close and indirect contact between humans. Lungs are the primary organ target of COVID-19, and its principal characteristic is pneumonia. The COVID-19 infection consists of three phases: asymptomatic phase, non-severe symptomatic phase, and severe symptomatic which is commonly followed by ARDS (acute respiratory distress syndrome). Pulmonary edema, acute hypoxia, and inflammatory cell buildup in the lungs are all symptoms of ARDS, which leads to cytokine storm. The proinflammatory cytokines that involve in ARDS are interleukin-1, tumor necrosis factor (TNF)-α, and IL-6. The increased number of macrophages, neutrophils, and T cells may contribute to trigger ARDS, multiple organ dysfunction syndromes (MODS) and failure of the coagulation system. Severe hypoxia caused by ARDS and MODS is one of the common causative deaths in COVID-19 patient.

Keywords: COVID-19, COVID-19's variant, ARDS, MODS, Cytokine storm.

Corresponding Author:
Retno Pudji Rahayu
Email: a-retno-p-r@fkg.unair.ac.id
Tel: +62-315030255

INTRODUCTION

Adequate immune system is required for protection against pathogens. SARS-CoV-2 that was firstly appear in Wuhan, China, has been widely spread across the globe. It is transmitted through contact with infected patients. COVID-19 was firstly reported as pneumonia with unknown etiology (1-4).

The World Health Organization considered COVID-19 as pandemic in 2020. COVID-19 approximately has infected 491 billion of people worldwide, with 6.15 billion of them leads to mortality. The lower part of lungs is the main target of SARS-CoV-2 in patients with pneumonia. There are four major proteins of SARS-CoV-2: spike protein (S), nucleocapsid (N), film (M), and envelope (E). The S protein is associated with initial virus entry. It mediates the virus to bind with angiotensin converting enzyme (ACE) - 2 (5-10).

There are currently four types of COVID-19 variants: variant of interest (VOI) and a variant of concern (VOC), as shown in table I. COVID-19 VOCs consist of: alpha, beta, gamma, and delta variants, while the COVID-19 VOIs consist of: Eta, Lota, Kappa, and Lambda variants. The Delta variant was firstly appeared in Maharashtra City of India in 2021, followed by the Omicron variant in South Africa on November 24, 2021. All VOIs and VOCs have mutations in D614G. The variants are associated with fast and severe progression of the COVID-19. The Omicron variant have transformations in its primary and non-primary proteins. There are 32 kinds of transformations in the underlying protein spike protein, with 15 of the 32 types of mutation found in the Receptor-Binding Domain (RBD). The non-structural protein encoded by ORF1ab contains transformations in nsp. Nsp3 and nsp 5 are proteases that divide. The polypeptide encoded by ORF1a and 1b, nsp12 is an objective for - obstructing drugs polypeptide that

Table I. Variant of Concerns (VOCs) and Variant of Interests (VOIs)

Type of Variants			
	A variant of Concerns (VOCs)		
	Variant Alpha	B.1.1.7 lineage status VOC-20DEC-01	Mutation occurs in Protein Spike (S) so that character is resistant to neutralizing antibodies (NAbs) obtained from convalescent plasma and individuals who have been vaccinated.
	Beta Variant	B.1.351 lineage status VOC-20DEC-02	
	Gamma Variant	P.1 lineage status VOC-21JAN-02	
	Variant Delta	B.1.617.2/AY.1/ AY.2 lineage status VOC-21APR-02	
	A variant of Interests (VOIs)		
	Variant Eta	B.1.525 lineage (VUI-21FEB-03) and B.1.1318 lineage (VUI-21FEB-04)	Mutation occurs in Protein Spike (S) so that character is resistant to neutralizing antibodies (NAbs) obtained from convalescent plasma and individuals who have been vaccinated
	Lota Variant	B.1.526 lineage	
	Kappa Variant	B.1.617.1 lineage	
	Variant Lambda	C.37 lineage	

separates and incorporates viral proteins (11-15).

The COVID-19 is divided into three phases: asymptomatic, non-severe symptomatic non-severe in the respiratory tract part top, and severe symptomatic phase. The non-severe symptomatic phase is commonly occurred in the upper respiratory tract, while the severe symptomatic phase is commonly occurred in lower respiratory tract, which is identified as acute respiratory distress syndrome (ARDS).

ARDS is a major causative fatality COVID-19. It is recognized by inflammation, increased cytokines secretion, and higher level of proinflammatory chemokines. The clinical features of ARDS are: acute pulmonary edema, hypoxemia, and ventilator-mediated breathing. ARDS is often linked with diffuse alveolar damage and injured epithelium of alveolar lung that may lead to accumulation of fluid protein-rich edema in the alveolar space. The cytokine storm, which is the resulted from enhanced inflammation response, is characterized by proinflammatory cytokines, Multiple Organ Dysfunction Syndrome (MODS), and death in severe COVID-19 cases. The cytokine storm is defined as systemic inflammation in response to various factors that interfere homeostatic processes (16-20).

METHODS

Sources from PubMed database, Research Gate, national journal, and international journal were used in this study. Articles about COVID-19-its transmission, response immune in COVID-19, Acute Respiratory Distress Syndrome (ARDS), the pathogenesis of ARDS, the emergence of cytokine storm and Multiple Organ Disorder Syndrome (MODS) as ARDS manifestations were included.

Search strategies

Literature search was conducted from January to April 2022 to identify published studies about transmission mechanism of COVID-19, immune response in COVID-19, acute respiratory distress syndrome (ARDS), the pathogenesis of ARDS, the emergence of cytokine storm and Multiple Organ Disorder Syndrome (MODS) as ARDS manifestations. Searching strategies focused on medical referencing from ScienceDirect, PubMed and Google Scholar. A mix of words and controlled vocabulary (COVID-19 AND Acute Respiratory Distress Syndrome (ARDS) AND cytokine storm AND Multiple Organ Disorder Syndrome (MODS) AND Mortality) were used. Inclusion criteria of this study is articles related to COVID-19, Acute Respiratory Distress Syndrome (ARDS), cytokine storm, Multiple Organ Disorder Syndrome and its effects on host's mortality. Exclusion criteria of this study is articles that only contains abstract; letters to the editor; editorials; patient handouts.

Figure 1 shows the four-phase Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram could establish the number of studies identified, screened, and included in the systematic review.

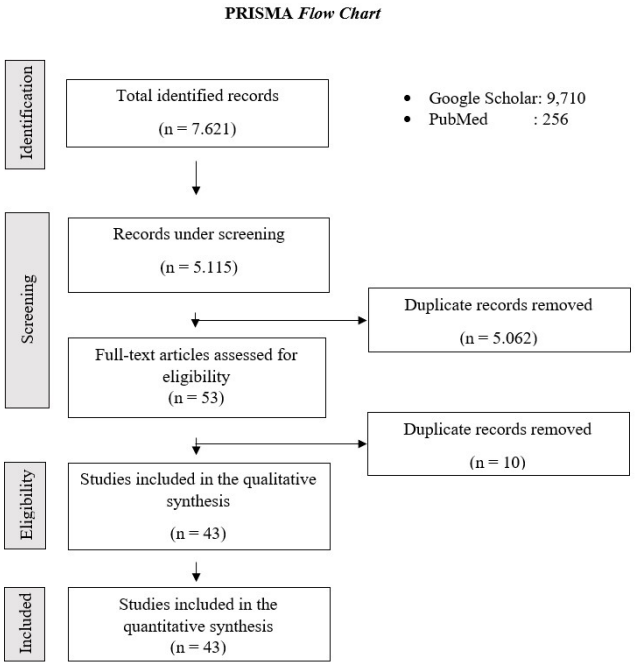

Fig. 1: . Flow diagram of study identification.

DISCUSSION

COVID-19 aerobiology pathway of communicable respiratory disease and its transmission in dentistry

The human-to-human transmission mechanism of COVID-19, consists of: secreted droplets from infected patients that directly contacts to mucosa, physical contact with droplets on surface area, inhaled aerosolized

droplets from respiratory system and secreted to the air. The first two routes transmit COVID-19 through droplets or contact, while the latter route is transmitted airborne. The airborne transmission is associated with tiny droplets that last for certain period of time. The droplets could migrate into great distance from the infected person (21).

The transmission of COVID-19 is initiated by virus atomization in infected individual to produce droplet containing viral spectrum. This droplet atomization begins in fluid lining within respiratory tract and it is formed from instable and fragmented mucous lining due to airflow-inducted shear stress. The size and distribution of droplets may vary because fragmentation process is relied on mucous as viscoelastic shear-thinning fluid. Droplets that were not reabsorbed migrated to respiratory airflow and removed through buoyant jet phase performed during breathing and talking. The speed of secreted droplets transport is in 5m/s speed. Small droplets are considered as indirect transmission mechanism of COVID-19.

The variants of droplets are: large droplet and small droplet. Both kind of droplets are affected by Stokes Theory of gravitational and force aerodynamic, which the trajectory particles are rely on their size and balance force of particles in the air. Gravitational forces are associated with enlarged mass and particle size. Large droplets tend to be more stable compared to small droplets that are more likely to develop into airborne (22).

Evaporation of droplets and droplet nuclei consist of the differences of droplet evaporation speed are influenced by droplet surface saturation vapor pressure, humidity, diffusion mass coefficient (the difference of speed between droplets and surrounding gas). High temperature and low humidity level increases droplet evaporation speed that may produce critical size droplet. The changes of temperature are also affected by survivability of SARS-CoV-2. The airborne transmission is associated with micro-size droplet that circulate in the air. Droplets may evaporate within seconds to develop into droplet nuclei. However, the buoyant turbulent expiratory jet may reduce the evaporation rate. Droplet nuclei circulate has one hour half-life circulate in the air in the form of multiple virions, solid residue, and water. The water particle could not be completely removed. The transmission is regulated by ambient flow and indoor environment so an adequate ventilation is needed to control airborne transmission of COVID-19.

The particles may be directly expelled and indirect aerosolization. Particles respiratory tracts could be directly expelled from infectious individual through coughing, sneezing, or normal breathing. The particles size may vary from 0.1 until 100 μm. Infectious agent may be indirectly aerosolized by contaminated air. The particles that circulate in the air is influenced by their initial size, composition, and environmental factor. The particles are mostly located in upper and lower respiratory tracts (23,24). Aerosol contains of particles that circulate in the air with size of less than 50 μm. Aerosol is divided into tiny and large droplet. The tiny droplets are easily evaporated to form droplet nuclei and migrate to other locations. Particles that are less than 0,5-10 μm in size tend to penetrate into lungs and cause disease (25).

Aerosols are normally produced during talking, breathing, sneezing, or coughing. Aerosol could reach 5 m/s speed and transport up to 6 meters in 0.12 seconds during sneezing. Droplets are transmitted within radius 1,5 to 2 meters. Aerosols contain fungi, bacteria, and/or virus. Humans are exposed to aerosol through physical contacts of skin, eye, and respiratory tract. The concentration of aerosol is measured by analyzing air sample. Aerosol are transmitted in the air with high indoor concentration of aerosol (26-30).

Immune Response in COVID-19

The virulence of Coronavirus in host is initiated by attachment and invasion of COVID-19 particle into the mucosa. It is mediated by protein S1 that binds to Angiotensin Converting Enzyme-2 (ACE-2) receptors. The ACE-2 receptors are widely distributed in human body, but SARS-CoV-2 is specifically bind to ACE-2 receptors in the upper respiratory tract (16,17). The binding of S1 with ACE-2 receptors is also influenced by cathepsin A/B, TMPRSS2, and the compatibility of Receptor binding Domain (RBD), Receptor Binding Motif (RBM), dan Transmembrane Domain (TD) between Spike S1 and ACE-2 receptors (18,19). Blocking on influencing elements S1 to ACE-2 virulence inhibit S1 to connect to ACE-2 despite the fact that ACE-2 is a receptor from S1 coronavirus (31,32). After binding of S1 and ACE-2 receptors, the Spike S2 invades ribosome in endoplasmic reticulum (ER) that is required for transcription and translation. Host response to S2 invasion by activating Antigen Presenting Cells (APC) that involve in COVID-19 (20,21).

The APCs consist of macrophage, mannose binding lectin (MBL), and dendritic cells (DC) are responsible of phagocytosis SARS-CoV-2 particles, and to present it to the B cells and T cells. DC bridges the innate and adaptive immune response through Toll Like Receptor (TLR)-3, TLR-7, TLR-8, TLR-9, c-type lectin, dan Pattern Recognition Receptors (PRRs) to identify Pathogen Associated Molecular Patterns (PAMPs) and viral RNA/DNA contained in endosome. Moreover, viral RNA induces Melanoma Differentiation-Associated gene 5 (MDA5) receptors and cyclic GMP-AMP nucleotidil transferase sintase (cGAS) that are responsible to identify viral RNA or DNA in cytoplasm. Both receptors form adaptor signaling complex that consist of: TIR-domain-containing adaptor protein including TNF-β (TRIF), Mitochondrial-Antiviral Signaling Protein (MAVS), and

Stimulator of Interferon Genes protein (STING). They act synergistically initiate molecular cascade of Myeloid differentiation-88 (Myd88) to produce Nuclear Factor Kappa Beta (NF-KB), interferon regulatory factor-3 (IRF-3), interferon αβ, and other pro-inflammatory cytokines (22,23).

NF-κB activate Intracellular Adhesion Molecule-1 (ICAM-1) to increase vascular permeability and lead to vascular edema. Warning signal from DC causes T helper (Th) cell to polarize and differentiate into Th1 and Th2 cells. The Th1 cells are derived from CD4+ cells that differentiated into Th1 and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF). SARS-CoV-2 releases viroporine after being presented by DC to activate inflammasome that consist of Nucleotide-binding domain, leucine-rich-containing-family, pyrin-domain-containing 3 (NLRP3). The activation of NLRP3 induces pro Interleukin 1β (pro IL-1β) turns into IL-1β (33,34).

The migration of DC from lymph node and differentiate into APC induce adaptive immune response to release cytokines and chemokines against SARS-CoV-2. Cytokines that were released during COVID-19 are: 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-2, IL-7, Granulocyte Colony Stimulating Factor (GCSF), and TNF-α. Chemokines that were released during COVID-19 are: CCL-2, CCL-3, CCL-5, CXCL-8, CXCL-9, and CXCL-10. The signal from APC to B cells are classified as adaptive humoral immune response that are indicated by increased level of Immunoglobulin G and M (IgG and IgM) (24,25,35).

Pathogenesis of COVID-19, acute respiratory distress syndrome (ARDS) leads to Cytokine Storm, Multiple Organ Dysfunction Syndrome (MODS), and Death

The pathophysiology of cytokine storm, MODS and death are initiated with the interaction of Spike1 protein with host angiotensin-converting enzyme (ACE)-2 (36). It is followed by interaction of Spike S2 protein subunit transmembrane serine protease 2 (TMPRSS2) and cathepsin B/L (CatB/L). After endocytosis or fusion with membrane cell surface, the viral genome remains in cytoplasm. The viral genome hijack translational process of host and produce polyprotein. Virus starts to spread to lower respiratory tract through aspiration or local infected cells within respiratory tract. The spike protein causes immune evasion because is highly immunodominant. Immune evasion is caused by mutation in N terminal domain (NTD) that is connected with escape neutralization (37).

Virus that penetrates into host cell trigger immune response, such as: (1) Viral Pathogen-Associated Molecular Patterns to produce pro-inflammatory cytokines and activation of pattern recognition receptor (PRR) by toll-like receptor (TLR). Interleukin-6 (IL-6) was released to activate nuclear factor kappa-beta (Nf-κB). (2) Inflammation as response to Spike S1 that binds with ACE-2. Increased Angiotensin II activate Nf-κB pathway through angiotensin type II receptor (AT1R). It produces high level of IL-6. AT1R is associated with ADAM10 and ADAM17 activation to produce tumor necrosis factor (TNF)-α and soluble interleukin 6 receptor (sIL-6Rα). That response causes inflammation cascade system of Nf-κB and STAT-3 signaling pathways that lead to excessive IL-6, which is called IL-6 amplifier (IL-6 AMP). The IL-6 AMP causes cytokine storm that leads to acute respiratory distress syndrome (ARDS), pneumonia, multi-organ dysfunction, and vascular coagulation (37). The ARDS is manifestation of hyperinflammation and leukocytes dysfunction. Hyperinflammation is associated with neutrophils that involve to eliminate pathogens, while clinically it is associated with severe COVID-19 through cytokine storm mechanism. The interaction of host with virus is mediated through pathogen-associated molecular patterns (PAMPs). Host immune system uses pattern recognition receptors (PRRs) in immune cells to identify PAMP. The TLR and PRR send viral danger-associated molecular patterns (DAMPs) signal to identify PAMP. Stimulated TLRs eliminate viral infection by activating Nf-κB pathway to produce IL-1, tumor necrosis factor (TNF)-α, and IL-6 to recruit more leukocyte cells (38,39).

Neutrophils are classified as innate immune cells that has short lifespan. They act as vital effector cells due to their ability to quickly eliminate pathogen and sensitive to microbial signals. The antimicrobial properties of neutrophils are mediated by phagocytosis, degranulation, and Neutrophil Extracellular Traps (NETs) mechanism. Neutrophils that migrate from bone marrow may differentiate into active and inactive (quiescent) form. The NET formation is associated with large microbial size when ingestion is could not be performed. The NETs are produced from DNA fiber and protein inside neutrophils granules (40-42).

Chemoattractant that released by neutrophils recruits more neutrophils to eliminate pathogens. The cell membrane of neutrophils express receptor complex and adhesion molecules against ligands, such as: immunoglobulin, and molecule membrane for other cells. NET is defined as nucleic acid that form in spiderweb-like shape. It is covered by histone to resist virus. NET is exclusively developed during fungi and bacterial infection, while NETosis was produced for viral infection. NETosis is produced through ROS-independent mechanism involving nuclear chromatin lined with protein effector and activation of peptidyl arginine deiminase type IV (PAD4) (41,43).

The envelope part of neutrophil nucleus will disintegrate shortly after stimulation to mediate binding

between chromatins and granular protein. Chromatin condensation is stimulated by histone hypercullination, Myeloperoxidase (MPO) and neutrophil elastase (NE). It is followed by excessive NET formation that leads to damaged lung tissue by NE and MPO. NETosis markers are correlated with bacterial and local inflammation in lungs and pneumonia-associated ARDS. Increased NETs formation is the hallmark of chronic obstructive pulmonary disease in ARDS patients, and is commonly followed by multiple organ disfunction syndrome (MODS) (41).

Inflammation triggers thrombotic complication that reflects disease severity. Complement activation potentiates platelet/NET/tissue factor/thrombin axis during COVID-19. Aggregation of neutrophil-platelet are commonly found in blood sample of COVID-19 patients. MPO-DNA complex is excessively formed in COVID-19 patients, and NET amount is positively correlate with ARDS severity in COVID-19. NETosis is NET that contains DNA, extracellular histone modification, protease, and cytotoxic enzyme that induce neutrophil to localized lethal protein in infection site. NET induce NE to initiate immune response against virus. Increased NET released by neutrophil is influenced by certain stimulus by toxin, virus, TNF-α, and IL-8 (41). The growing amounts of neutrophils in alveolar cells release toxic mediators of NETs, protease, and ROS. NET is initially formed by neutrophils as part of immune response, but excessive NETs cause endothelial and epithelial injuries. Monocytes also penetrates into lungs and cause injury through tumor necrosis factor (TNF)-α pathway by inducing TRAIL and activation of cell death receptor. Activated platelets stimulates PMN aggregates that involve in NET formation (42).

Dentistry, dental schools, and hospitals-related dentistry have been also significantly affected by pandemic of COVID-19 because of their profession. They related to the very high risk or special danger of viral transmission because they are close to their both symptomatic/asymptomatic patients' mouth during the dental procedures because they work in environments contaminated with blood, saliva, and others body fluid through direct contact and produce aerosol termed aerosol generating procedures (AGPs). The COVID-19 virus contained in aerosol can either reside in the dentists' equipment or directly be expelled by the dentists during or after taking care their patients represented by Tissue-Culture Infectious Disease (TCID50) on several surfaces, namely: plastic (as long as for 72 hours), aluminium (as long as for 48 hours), copper (as long as for 4-8 hours), aerosol (as long as for 1.1-1.2 hours), and all of surfaces in dentistry materials. The level of TCID50 can be until 72 hours long before it enters the dentists' or their assistant body. These two pathways, then can cause the SARS-CoV-2 to enter the dentists and their assistants so that they are heavily susceptible to be infected by SARS-CoV-2. Once the virus enters the body, the dentists can undergo cytokine storm or ARDS depends on their adequate immunity to combat COVID-19 invasion (28,43).

CONCLUSION

Adequate immune response is required in COVID-19 infection because its severity is caused by excessive level of pro-inflammatory cytokines and chemokines that is called as cytokine storm. The storm may trigger lung injury and multiple organ dysfunction syndrome (MODS).

ACKNOWLEDGEMENTS

This article is supported by the Indonesian Ministry of Research and Technology, School of Postgraduate Immunology Division, Universitas Airlangga, and the Faculty of Dental Medicine, Universitas Airlangga, Surabaya.

REFERENCES

1. Meng L, Hua F, Bian Z. Coronavirus Disease 2019 (COVID-19): Emerging and Future Challenges for Dental and Oral Medicine. Journal of Dental Research. 2020: 1-7; DOI: 10.1177/0022034520914246journals.sagepub.com/home/jdr
2. Setiawan F, Sosiawan A, Wahjuningrum DA, et al. Corona Virus Disease 2019 (COVID-19) In Salus Populi Suprema Lex Esto Principle and Pathogenesis Study. Bandung: Haura Utama; 2020.
3. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Military Medical Research. 2020; 7(1): 1-10; https://doi.org/10.1186/s40779-020-00240-0
4. Nurdianto AR, Tena HAB, Setiawan F. Guidelines Short Practice Dentistry During the COVID -19 Pandemic. Sidoarjo: Nizamia Learning Centre; 2021.
5. Gaddam RR, Chambers S, Bhatia M. ACE and ACE2 in Inflammation: A Tale of Two Enzymes Inflamm & Allergy-Drug Targets. 2014;13: 1-12.
6. Hoffman M, Weber HK, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell Press. 2020; 181: 1-10; https://doi.org/10.1016/j.cell.2020.02.052
7. Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for the development of RBD protein as viral attachment inhibitor and vaccine. Nature: Cellular & Molecular Immunology. 2020: 1-8
8. Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis. Methods Mol

Biol. 2015; 1282, pp: 1-23, DOI: 10.1007/978-1-4939-2438-7_1
9. Singhai T. A Review of Coronavirus Disease-2019 (COVID-19). The Indian Journal of Pediatrics. 2020; 87(4):281-6; https://doi.org/10.1007/s12098-020-03263-6
10. Law HKW, Cheung CY, Ng HY, et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood. 2005; 106(7):2366-74
11. Mlcochova P, Kemp S, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant emergence and vaccine breakthrough. Biological SciencesArticle; https://doi.org/10.21203/rs.3.rs-637724/v1
12. Kimura I, Kosugi Y, Wu J, et al. SARS-CoV-2 Lambda variant exhibits higher infectivity and immune resistance. bioRviv preprint; https://doi.org/10.1101/2021.07.28.454085
13. Pinto OMC, Coronado SMC. Emergent SARSCoV-2 Variants; The Delta and Lambda Variants. In print
14. Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England. 2021
15. Shah M, Woo HG. 2021. Omicron: A heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escapes approved COVID-19 therapeutic antibodies. bioRxiv preprints:1-14; https://doi.org/10.1101/2021.12.04.471200
16. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respiratory Medicine, 2020: 1-4; https://doi.org/10.1016/S2213-2600(20)30076-X
17. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. Journal of Pharmaceutical Analysis. 2020; 1-17; DOI: https:/doi.org/10.1016/j.jpha.2020.03.001
18. Cheng VCC, Lau SKP, Woo PCY, Yuen KY. Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection. Clin Microbiol Rev. 20(4): 660-94, doi:10.1128/CMR.00023-07
19. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2 Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. Virology Sinica. 2020: 1-6; https://doi.org/10.1007/s12250-020-00207-4
20. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004; 136:95-103; doi:10.1111/j.1365-2249.2004.02415.x
21. Mittal R, Ni R, Seo JH. 2020. The flow physics of COVID-19. J Fluid Mech; 894:F2-1:F2-14; doi:10.1017/jfm.2020.330
22. Lipinski T, Ahmad D, Serey N, Jouhara H. 2020. Review of ventilation strategies to reduce risk of disease transmission in high occupancy buildings. International Journal of Thermofluids; 2020:100045; https://doi.org/10.1016/j.ijft.2020.100045
23. Seminara G, Carli B, Forni G, Fuzzi S, Mazzino A, Rinaldi A. Biological fluid dynamics of airborne COVID-19 infection. Rendiconti Lincel. Scienze Fisiche e Naturali. 2020; 31:505-37; https://doi.org/10.1007/s12210-020-00938-2
24. Bourouiba L. Fluid Dynamics of Respiratory Infectious Diseases. Annual Review of Biomedical Engineering. 2021;23:547-77; http://dx.doi.org/10.1146/annurev-bioeng-111820-025044
25. Innes N, Johnson IG, Al-Yaseen W, et al. A systematic review of droplet and aerosol generation in dentistry. Journal of dentistry. 2021; 105, 103556. DOI: 10.1016/j.jdent.2020.103556.
26. Law S, Leung AW, Xu C. Severe acute respiratory syndrome (SARS) and coronavirus disease-2019 (COVID-19): From causes to preventions in Hong Kong. International Journal of Infectious Diseases. 2020; 94: 156–63. DOI: 10.1016/j.ijid.2020.03.059.
27. Nguyen LH, Drew DA, Graham MS, et al. A prospective cohort study is on the risk of COVID-19 among front-line healthcare workers and the general community. The Lancet Public Health. 2020; 5(9): e475 - e483. DOI: 10.1016/S2468-2667(20)30164-X.
28. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res. 2020;188: 1-19, HTTPS://doi.org/10.1016/j.envres.2020.109819
29. Setiawan F, Yudianto A, Sunariani J, Mooduto L. New Normal to Achieve High Threshold Herd Immunity by (Ro and Pc) Post Pandemic COVID-19. MJMHS. 2021; 17(2):141-5
30. Block B, Malizia F, Druenen Tv, Marchal T. 2020 Towards aerodynamically equivalent COVID-19 1.5 m social distancing for walking and running
31. Rosti ME, Olivieri S, Cavaiola M, Seminara A, Mazzino A. Fluid dynamics of COVID-19 airborne infection suggest urgent data for a scientific design of social distancing. Scientific Reports. 2020; 10: 22426 https://doi.org/10.1038/s41598-020-80078-7
32. Wang C, Xie J, Zhao L, et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. EbioMedicine. 2020;57:102833; https://doi.org/10.1016/j.ebom.2020.102833
33. Lukan R. "Cytokine storm", not only in COVID-19 patients. Mini-review. Immunology Letters. 2020;228:38-44; https://doi.org/10.1016/j.imlet.2020.09.007
34. Rosa GL, Fratini M, Libera SD, Iaconelli M, Muscillo M. Viral infections are acquired indoors through airborne, droplet or contact transmission. Ann 1st Super Sanita. 2013; 49(2): 124-32
35. Nile SH, Nile A, Qiu J, Li J, Jia X, Kai G. COVID-19:

Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine and Growth Factor Reviews. 2020; 53: 66-70; https://doi.org/10.1016/j.cytogfr.2020.05.002
36. Hartenian E, Nandakumar D, Lari A, Ly M, Tucker JM, Glaunsinger BA. The molecular virology of coronaviruses. Journal of Biological Chemistry;295(37):12910-34
37. Hojyo S, Uchida M, Tanaka K, et al. How COVID-19 induces cytokine storm with high mortality. Inflammation and Regeneration. 2020;40:37 https://doi.org/10.1186/s41232-020-00146-3
38. Chen IY, Moriyama M, Chang MF, Ichinoche T. Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. Frontiers in Microbiology. 2019; 10(50): 1-9; DOI: 10.3389/fmicb.2019.00050
39. Zhou Y, Fu B, Zheng X, et al. Pathogenic T Cells and inflammatory monocytes incite inflammatory storm in secure COVID-19 patients. Downloaded from https://academic.oup.com/nsr/advance-article-bstract/doi/10.1093/nsr/nwaa041/5804736 by Kangwon National University, Samcheok Campus user on March 21, 2020
40. Nurdianto AR, Budiningsih AT, Marthawati S. Complications of Pulmonary Embolism in Corona Virus Disease 2019 (Covid-19): A Literature Review. Journal of Pharmaceutical Care Anwar Medika. 2021;4(1):1-19
41. Borges L, Curi TCP, Curi R, Hatanaka E. COVID-19 and Neutrophils: The Relationship between Hyperinflammation and Neutrophil Extracellular Traps. Hindawi Mediators of Inflammation. 2020; 2020:1-7; https://doi.org/10.1155/2020/8829674
42. Fajgenbaum DC, June CH. Cytokine Storm. The New England Journal of Medicine. 2020;383:2255-73; DOI:10.1056/NEJMra2026131
43. Setiawan F, Puspitasari H, Sunariani J, Yudianto A. Molecular Review of COVID19 From the Pathogenesis and Transmission Aspect. Journal of Environmental Health. 2020;12(1):1-11; DOI:10.20473/ jkl.v 12i1si.2020.93-103