Review Article

Risk of coronavirus disease 2019 (COVID-19) infection on leukemia patients: basic science to clinical aspect

Agung Firmansyah Sumantri[1,2], Muhammad Hasan Bashari[3,4], Hilman Tadjoedin[5], Nur Atik[3,4*]

[1] Postgraduate Program, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia. [2] Department of Internal Medicine, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia. [3] Department of Biomedical Sciences, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia. [4] Oncology and Stem Cell Working Group, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia. [5] Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.

Correspondence: Nur Atik, Department of Biomedical Sciences, Faculty of Medicine, Padjadjaran University, Bandung, West Java, 40161, Indonesia. n.atik@unpad.ac.id

ABSTRACT

In March 2020, the Coronavirus disease 2019 (COVID-19) pandemic was announced by the World Health Organization (WHO). A novel strain of coronavirus, recently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) created the disease, which showed symptoms similar to SARS. The virus's bond determines its pathogenesis with its host's cell receptors, mainly the Angiotensin-Converting Enzyme 2 (ACE2). It is a factor of the Renin-Angiotensin System (RAS), that holds a vital function in hematopoiesis of hematologic malignancies. There is mRNA expression of the RAS component, so there is an increase in ACE2 levels in patients with leukemia, primarily the myeloid type. Acute Myeloid Leukemia (AML) malignant blood cells can escape from the immune system through a biochemical mechanism that causes AML cells to deactivate Natural Killer (NK) and cytotoxic lymphoid cells (cytotoxic T cells (CTC). This review article aims to explain the molecular mechanism, including leukemia patients' immune system with COVID-19 and recommendations for patients and hemato-oncologists.

Keywords: ACE2, COVID-19, Immune system, Leukemia, SARS-CoV

Introduction

The coronavirus pandemic has become a universal well-being matter. The virus spread all over the world and still has not stopped, after reporting the first case in Wuhan, China, in December 2019. The most recent data recorded that the virus has spread and contaminated above 700 thousand people and has caused the death of above 36 thousand patients worldwide [1-4]. Previous research stated that the virus had been found in Chinese horseshoe bats. A wet market in Wuhan where wild animals were sold as food or pets has been suspected to be the epicenter of this outbreak [5].

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Sumantri A F, Bashari M H, Tadjoedin H, Atik N. Risk of coronavirus disease 2019 (COVID-19) infection on leukemia patients: basic science to clinical aspect . J Adv Pharm Educ Res. 2022;12(1):38-45. https://doi.org/10.51847/qqIktBAHB7

The etiology of COVID-19 is transmitted through droplets or small particles coming out of a sick person's mouth (saliva) containing the virus [6]. The cases reported in Italy confirmed that patients who die are in their 80s, while in China, it is the patients in their 60s. It means the older a person, the more contributing diseases they have, the worse their conditions would be if the virus infected them. In the elderly, there is a decrease in T cell and B cell production in the bone marrow and thymus. There is also a decrease in mature lymphoid function in secondary lymphoid tissues. These cause the immune response in the elderly not to be as strong as that of a young person [7]. Besides that, other conditions that cause people to have a higher risk of death when infected with coronavirus are comorbidities such as chronic respiratory diseases, diabetes mellitus, coronary artery disease, hypertension, and cancer included hematologic malignancy, especially leukemia [8]. This review will discuss the pathophysiology of leukemia and its correlation with the SARS-CoV-2 infection susceptibility. Additionally, the study will enlighten the hemato-oncologist to protect their patients in the recommendation part.

Epidemiology of COVID-19 and Leukemia

Currently, in China, where the first case of COVID-19 was found, 82.545 positive cases and 3.314 deaths due to COVID-19 have been recorded [2]. The first case in China was reported in Wuhan, Hubei Province, and then cases kept appearing in other provinces around Hubei [7, 9].

All over the world, 198 countries have reported positive cases of COVID-19 and 158 countries with local transmission. WHO's most recent report stated 750.890 confirmed cases and 36.405 deaths from COVID-19 [2]. The country with the most confirmed cases in the United States of America, with 161.199 verified cases and 2.850 deaths [3]. In March 2020, due to a high number of confirmed cases and deaths worldwide, the World Health Organization announced COVID-19 as a pandemic [1].

Leukemia is a malignancy that is commonly found in children and adults. The four major subtypes of leukemia most widely found are acute lymphoblastic leukemia (more common in children), chronic myelogenous leukemia, chronic lymphocytic leukemia, and acute myelogenous leukemia [10]. Leukemia causes more deaths in men (cumulative risk 0,40%) than women (cumulative risk 0,26%) [11].

The GLOBOCAN report in 2018 stated there were 437.033 new cases of leukemia globally and caused 309.066 deaths. According to the observational data, leukemia as the 13th malignancy with the most significant number of new cases and the tenth-largest malignancy cause of death in 2018 [11].

Virology of SARS-CoV

COVID-19 is a respiratory disease resulted by the novel coronavirus [12]. Its beta coronavirus has an envelope including a positive single-stranded RNA genome (26-32 kb) **(Figure 1)** [13-15]. The International Committee on Taxonomy of Viruses (ICTV) announced this new coronavirus had been named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 2020 [13, 14]. Human coronaviruses belong to the alpha (HCoV-229E and NL63) and beta (HCoV-HKU1, SARS-CoV, MERS-CoV, and HCoV-OC43) coronavirus genera [16, 17]. B-CoV was found in all pneumonia patients admitted from 18 to December 29, 2019, in China. The 88% of isolated b-CoV showed identities of viruses from bats, the Severe Acute Respiratory Syndromes (SARS)-like coronaviruses, and approximately 50% were MERSCoV [18].

Coronavirus is a zoonotic pathogen with a high mutation level and is a pleomorphic RNA virus with a crown-like peplomer sized 80-160 nM [19-21]. The SARS-CoV-2 genome is like CoV, with 10 open reading frames (ORFs). The first two-thirds of ORFs (ORF1a/b) encodes virus polymerase (RdRp), an RNA synthesis material, and two non-structural polypeptides which are not involved in host modulation response (ORF1a-ORF1b) [22]. Another one-third of SARS-CoV-2's ORFs encodes 4 structural proteins, nucleocapsid protein (N), the spike protein (S), membrane protein (M), an envelope protein (E), and several additional proteins that function in virus replication are still unknown. The Angiotensin-Converting Enzyme 2 (ACE2) is needed as a receptor to fuse the SARS-CoV-2 and its host cell **(Figure 2)**. The bond between virus and host cell receptors determines the pathogenesis of infection [23-26].

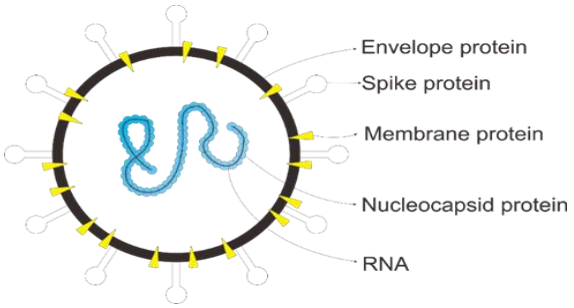

Figure 1. SARS-CoV-2 Structure. (Taken with Modifications from Peiris *et al.*, 2003) [26]

Pathophysiology of myeloid leukemia

Acute leukemia is an aggressive blood malignancy characterized by the accumulation of pathological hematopoiesis progenitors [27]. Leukemia can be caused by benzene, some chemotherapy drugs classified as alkylating agents, radiation, and the underlying hematological disorders. Acute Myeloid Leukemia (AML) is a disorder caused by abnormal proliferation and differentiation of stem cells that causes an increase in the number of myeloid progenitors in the bone marrow and peripheral blood to produce abnormal granulocytes [28]. Myeloid cells in AML continue to be produced, but cell maturation does not occur, so many abnormal cells are formed. This causes the cumulation of leukocytes in the bone marrow that negatively impacts the function of platelets and red blood cells.

Changes in the normal maturation procedure of precursor cells are caused by the translocation of chromosomes t(8; 21) on a core-binding factor of AML or t(15; 17) on Acute Promyelocytic Leukemia (APL), which produces PML-RARA and chimeric proteins (RUNX1-RUNX1T1). Several studies classify various mutations associated with AML. Class I mutations must coincide with class II mutations so that leukemia can occur. Class I mutations include internal tandem duplications/ITD), c-KIT, FLT3, K/NRAS, TP53, and Tyrosine Kinase Domain mutations/TKD). In addition, there is the role of signal transducer and activator of transcription 3 (STAT3) in stimulating cell proliferation and survival. Class II mutations include CEBPA and NPM1. Mutations of genes related to DNA methylation, IDH-1/IDH-2, TET2, and DNMT3A, were detected in 40% of AML cases, known as class III mutations. C-KIT mutations are related to t (8; 21) or inv (16), whereas NMP1 (class II mutations) often occur together with class I FLT3-ITD mutations or epigenetic mutations of IDH-1, IDH-2, and DNMT3A [29].

AML cells can escape immune attacks through biochemical mechanisms that cause deactivation of cytotoxic lymphoid cells by AML cells. AML cells have the capability for expressing surface proteins, including ligands of cytotoxic T-cell antigen 4 (CTLA4), receptor ligands (PD-Ls) 1 and 2, and programmed death-1 (PD-1). PD-Ls 1 and 2 interact with PD-1 on the surface of lymphoid cells and cause helper T cells to stop forming IL-2

needed for CTC and N.K. cell activation. This results in the inactivation of CTC and N.K. cells, causing these cells to lose the potential to kill AML cells. AML also expresses the neuronal receptor latrophilin 1 (LPHN1). LPHN1 is usually expressed in hematopoietic stem cells and disappears after maturation. LPHN1 in AML simplifies Tim-3-galectin-9 exocytosis so that cells can survive. Galectin-9 interacts with CTC and N.K. cells, causing a reduction in N.K. cell cytotoxic activity and CTC killing. N.K. cells will produce interferon-ɣ (IFN-ɣ) and induce IDO1 activation (indoleamine 2,3-dioxygenase). Formil-L-kynurenine will be degraded to L-kynurenine, which damages N.K. cytotoxic activity. IFN-ɣ also affect the induction of the PD-Ls which can increase the protection capability of AML cells from immune surveillance [30].

Manifestations of COVID-19 in patients without and with leukemia

The incubation period of COVID-19 can be up to 3-14 days, five days on average [31]. During the initial phase, it does not show any symptoms, and the blood tests show normal or slightly decreased leukocyte and lymphocyte count. SARS-CoV-2 will spread to the lungs, digestive system, and heart. Those tissues express ACE2, which plays a significant role as host cells receptor for SARS-CoV-2. Coronavirus spreads through blood and causes the common COVID-19 symptoms, such as productive cough, difficulty breathing, fever, nasal congestion, sore throat, hemoptysis, and diarrhea [32-36]. Most patients' peak temperatures are between 38,1-39°C and mostly show respiratory symptoms [32].

If the disease is left untreated, the disease course may cause uncontrolled inflammatory processes leading to complications such as Acute Respiratory Distress Syndrome (ARDS) and sepsis that can result in death [7]. From initial symptoms to death, it may take 6-41 days, 14 days on average. The duration depends on the patient's age and immunity status [35]. Patients' CT-Scan show ground-glass appearance in the subpleural regions of both lungs. Other radiographic images show infiltrations in upper lung lobes that are associated with severe dyspnea and hypoxemia [33].

China has reported a leukemia patient presenting with a fever for four days, sore throat, productive cough, and difficulty breathing. Clinical examinations reveal an increase in body temperature, leukocytosis, lymphocytosis, hemoglobin, and thrombocytopenia. CT-Scan images showed an opaque ground glass appearance and a small amount of fluid in the pleural sac. The hematological parameters of leukemia patients can decrease the suspicion of infection since processes cause the increased leukocyte in leukemia [37].

COVID-19 patients with cancer as comorbidity are at higher risk of experiencing severe symptoms requiring more intensive care with a higher mortality rate. Seven out of 18 (39%) COVID-19 patients with cancer as comorbidity required ventilators, and it is higher than COVID-19 patients without cancer comorbidities who have to use ventilators (124 out of 1572 patients (8%)) [38]. Currently, no studies have reported an increased susceptibility to getting infected with SARS-CoV-2 in patients with leukemia.

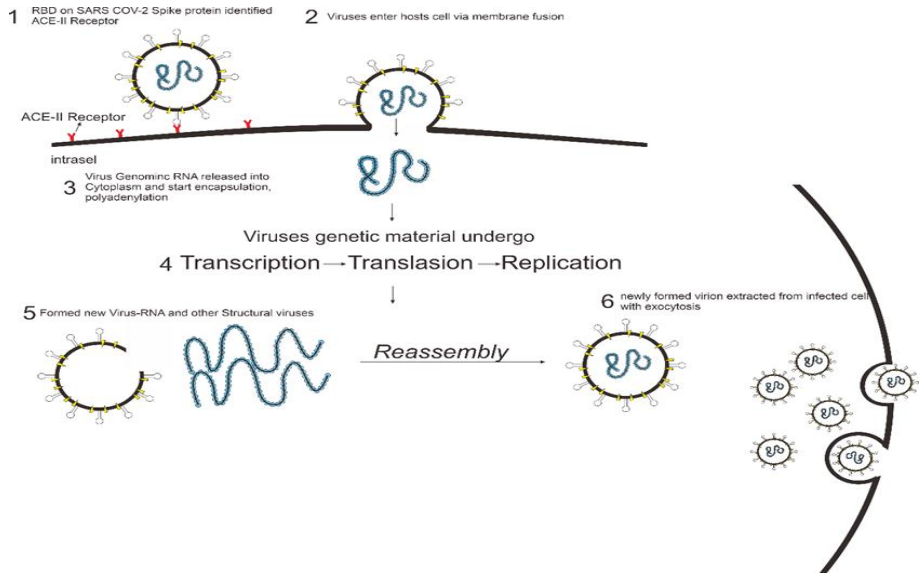

Figure 2. Molecular Mechanism of SARS-CoV-2 Infection. (Taken with Modifications from Koestler, 2020) [39]

Renin-Angiotensin system (RAS) in leukemia mechanism

ACE2, as the host cell receptor for SARS-CoV-2, significantly affects the pathobiology of leukemia. ACE2 is one of the many component molecules of the Renin-Angiotensin System (RAS). In addition to ACE 2, RAS has several other molecules, namely angiotensinogen (ANGTS), angiotensin receptors (AT1R and AT2R), and AcSDKP. These RAS molecules are found within the bone marrow and compartment cells [40]. RAS has an important role in hematopoiesis, apoptosis, cell proliferation, intracellular signaling, mobilization, angiogenesis, fibrosis in cytokine tissue, and other pathobiologies [41]. Malignant neoplastic blood cells

originate from stem cells in pathological proliferative process [40].

Bone marrow RAS plays a role in embryonic hematopoiesis and the production of blood neoplasm [42, 43]. Angiotensin II (Ang II) will stimulate type 1 and type 2 angiotensin receptors (AT1/AT2) and then stimulate or inhibit the Janus-kinase-signal activator and transducer of transcription (JAK-STAT) pathway related to activities of hematopoietic cytokines during normal hematopoiesis and neoplastic myeloproliferation [44-46]. In lymphoid and myeloid leukemia, specific mRNA expressions of RAS components were detected [40, 46].

Malignancy and anticancer therapies cause systemic immunosuppressive state in cancer patients [38]. This condition decreases the body's ability to control virus replication and makes the viral shedding process longer [16]. These then lead to cancer patients being more susceptible to infections than people without cancer, and the recovery process takes longer with more severe symptoms [3].

COVID-19 molecular mechanism and immune reaction in patients with leukemia

SARS-CoV-2's molecular mechanism of infection is not currently well known, but it is thought to have similarities with SARS-CoV's mechanisms. The virus can interact with human cells through spike protein (S) for infection to occur. Genome coding and gene expression will occur following the successful interaction, increasing CoV's adaptation to humans as hosts. CoVs often undergo genome change due to recombination, gene change, gene insertion, or deletions, causing extreme events [24].

SARS-CoV enters its host's cell through fusion with the plasma membrane mediated by proteolytic activity of S protein (S2') [47]. glycoprotein spike (S) will bind with cellular receptor ACE2 and CD209L (lectin type C or L-SIGN) [48]. Aside from membrane fusion, SARS-CoV also enters the host's cell through clathrin-dependent and clathrin-independent endocytosis [49]. SARS-CoV's S protein has a receptor-binding domain (RBD) that recognizes ACE2 as the host cell's receptor [50-54]. Other researches show that the host's ACE2 affinity determines the host's susceptibility to SARS-CoV infection to RBD [55-59].

The RNA genome is released into the cytoplasm after successfully entering the cell. RNA genome will then undergo encapsulation and polyadenylation, then coding some structural and non-structural polypeptide genes [16-24]. RNA genome and virus proteins are then reassembled in virion form in the endoplasmic reticulum and the Golgi. Further, the genome is transported by vesicles that are going to fuse with the plasma membrane [60]. Next, infected cells will release virions via exocytosis. Released viruses can infect kidney, liver, digestive system cells, and T lymphocytes of the respiratory tract, causing signs and symptoms of COVID-19 [61].

Antigen will then be presented to Antigen Presentation Cells (APC), the antiviral immunity center [13]. The antigen peptide presented by Human Leukocyte Antigen (HLA) or Major Histocompatibility Complex (MHC) and will be recognized by virus-specific Cytotoxic T Lymphocyte (CTLs) [13]. SARS-CoV antigen presentation depends on the assistance of MHC 1 and MHC II molecules. Previous studies have shown that some HLAs are related to susceptibility to SARS-CoV, including HLA-Cw * 0801, HLA-B * 0703, HLA-DR B1 * 1202, and HLA-B * 4601. Additionally, the HLA-Cw1502, HLA-A * 0201, and HLA-DR0301 allele are associated with protection against SARS infection. It is also shown that polymorphism of the Mannose-Binding Lectin (MBL) gene related to antigen presentation is linked to the risk of SARS-CoV infection [61-64].

Antigen presentation will stimulate cellular and humoral immunity mediated by B cell and T cell [60]. Immunoglobulin G (IgG) and immunoglobulin M (IgM) are specific antibodies against SARS-CoV; both can be recognized in two weeks, reaching their peaks in 60 days and remaining up to 180 days after infection [65]. SARS-CoV can create irregularity in T cell antivirus response due to T cell apoptosis stimulation, resulting in a decrease of the immune system. Recent reports indicate that in some patients infected with SARS-CoV-2, there is a decrease in CD8 and CD4 T cells in their peripheral blood. CD8 and CD4 memory T cells survive up to 4 years in individuals recovered from SARS and can perform cell T proliferation, DTH response, and IFN-gamma production [66].

The increase of ACE2 level in leukemia causes the host's receptor for SARS-CoV to increase, leading to the hypothesis that patients with leukemia, especially the myeloid type, have higher risks of getting COVID-19, and it can be fatal **(Figure 3)**.

The most common complication of COVID-19 is ARDS. It is generally the main reason for death in patients with COVID-19 [13]. Cytokine storm, one of the many mechanisms causing ARDS, is an uncontrolled systemic inflammatory response caused by the release of chemokines (CCL2, CCL3, CCL5, etc.) in a large number by effector immune cells and pro-inflammatory cytokines (TNF-a, IL-18, IL-12, IL-6, IL-1b, IFN-g, IFN-a, etc.) during SARS-CoV infection [67-70]. Cytokine storm will trigger a massive immune system attack on the body, resulting in many organ failures leading to death in severe SARS-CoV infection cases [70].

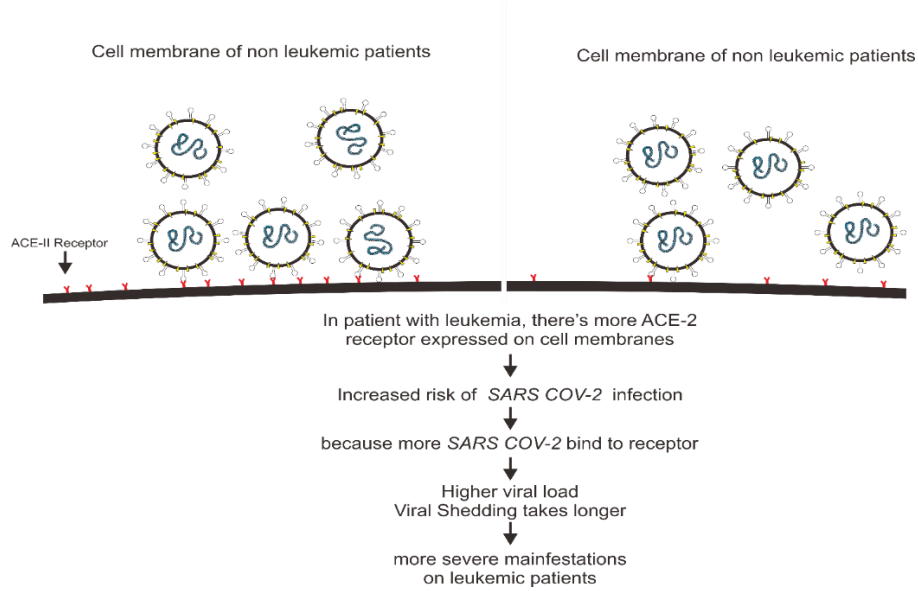

Figure 3. SARS-CoV-2 Infection on Patients with Leukemia

Conclusion

Patients with myeloid leukemia are more susceptible to be infected by SARS-CoV-2 because there are more ACE2, the receptors for SARS-CoV-2, in their bodies. ACE2 plays a role in myeloid malignant hematopoiesis. Viral shedding in patients with systemic immunosuppression, as in leukemia, takes longer. Therefore, the symptoms caused will be more severe in leukemia patients compared to patients without systemic immunosuppression.

Recommendation

It is highly recommended for patients to get COVID-19 vaccination when it is available. In the middle of this pandemic, prevention is necessary for patients with leukemia. All they need to do is maintain personal and environmental hygiene and keep the physical distancing.

A hematologist who will provide therapies such as chemotherapy or bone marrow transplantation is best if the SARS-CoV-2 tests are done on the patients first. If the tests are not available, testing can be done by screening and through chest C.T. imaging. If the test confirms that the patient is infected with SARS-CoV-2, the doctor should consider delaying systemic therapy if possible. Medications for leukemia that do not cause immunosuppression can be continued without any adjusting the dose.

Acknowledgments: This work was supported by grants from Padjadjaran University and the Ministry of Education, Culture, Research and Technology of the Republic of Indonesia to Nur Atik.

Conflict of interest: None

Financial support: This project was supported by grants from Padjadjaran University and the Ministry of Education, Culture, Research and Technology of the Republic of Indonesia.

Ethics statement: None

References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 – March 11, 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Kementerian Kesehatan Republik Indonesia. Info Infeksi Emerging Kementerian Kesehatan RI [Internet]. 2020 [updated 2020 April 1; cited 2020 April 2]. Available from: https://infeksiemerging.kemkes.go.id
3. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 72 [Internet]. WHO; 2020 [updated 2020 April 1; cited 2020 April 2]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2
4. Magomedova UG, Khadartseva ZA, Grechko VV, Polivanova MN, Mishvelov AE, Povetkin SN, et al. The Role of Covid-19 in the Acute Respiratory Pathology Formation in Children. Pharmacophore. 2020;11(5):61-5.
5. Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and don't. Microbiol Aust. 2020;41(1):45-50. doi:10.1071/MA20013
6. World Health Organization. Modes of transmission of the virus causing COVID-19: implication for IPC precaution recommendations. WHO; 2020. Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
7. Guzzi PH, Pedace E, Giorgi FM. Intersection between ageing-related Genes and SARS-CoV-2 Interactome: Is it

higher than expected?. 31 December 2020, PREPRINT (Version 2) available at Research Square. doi:10.21203/rs.3.rs-137634/v2

8. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-42. doi:10.1001/jama.2020.2648.
9. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan H, et al. Coronavirus disease 2019: Tinjauan literatur terkini. J Penyakit Dalam Indones. 2020;7(1):45-67.
10. Pandey P. Cancer of White Blood Cells: Blood Cancer. J Tum Res Rep. 2021;6:141.
11. The Global Cancer Observatory. Source: Globocan 2018. World Health Organization, 2019;876:2018-2019. Retrieved from https://gco.iarc.fr/today/data/factsheets/cancers/36-Leukaemia-fact-sheet.pdf
12. Center for Disease Control and Prevention (CDC). What You Need to Know about coronavirus disease 2019 (COVID-19). 2020. Choice Reviews Online, CS 314937-, 314937. doi:10.5860/choice.48-1502
13. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8. doi:10.1016/j.jpha.2020.03.001
14. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502. doi:10.1016/j.tim.2016.03.003
15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi:10.1056/NEJMoa2002032
16. Kesheh MM, Hosseini P, Soltani S, Zandi M. An overview on the seven pathogenic human coronaviruses. Rev Med Virol. 2021:e2282.
17. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. Biomed J. 2020;43(4):328-33.
18. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74. doi:10.1016/S0140-6736(20)30251-8.
19. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. J Microbiol Immunol Infect. 2021;54(2):159-63.
20. Sahin AR, Erdogan A, Agaoglu PM, Dineri Y, Cakirci AY, Senel ME, et al. 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature. EJMO. 2020;4(1):1-7.
21. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018;23(2):130-7.
22. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020;9(1):221-36.
23. Luk HK, Li X, Fung J, Lau SK, Woo PC. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. Infect, Genet Evol. 2019;71:21-30.
24. Coronavirinae in ViralZone. Available online: https://viralzone. expasy.org/785 (accessed on February 05 2019).
25. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):1-0
26. Zhang Q, Xiang R, Huo S, Zhou Y, Jiang S, Wang Q, Yu F. Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. Signal Transduct Target Ther. 2021;6(1):1-9.
27. Vakiti A, Mewawalla P. Acute Myeloid Leukemia. [Updated 2021 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507875/
28. Saultz JN, Garzon R. Acute myeloid leukemia: a concise review. J Clin Med. 2016;5(3):33.
29. De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Cancer J. 2016;6(7):e441.
30. Yasinska IM, Silva IG, Sakhnevych S, Gibbs BF, Raap U, Fasler-Kan E, et al. Biochemical mechanisms implemented by human acute myeloid leukemia cells to suppress host immune surveillance. Cell Mol Immunol. 2018;15(11):989-91. doi:10.1038/s41423-018-0047-6
31. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MU, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med. 2020;27(2):taaa008. doi:10.1093/jtm/taaa008.
32. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan H, et al. Coronavirus disease 2019: Tinjauan literatur terkini. J Penyakit Dalam Indones. 2020 Apr 1;7(1):45-67.
33. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J. 2020;133(9):1015. doi:10.1097/CM9.0000000000000722.
34. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5.
35. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020;92(4):441-7. doi:10.1002/jmv.25689.

36. Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-nCoV) Coronavirus. Am J Respir Crit Care Med. 2020;201(4):P7-8. doi:10.1164/rccm.2014P7.
37. Jin XH, Zheng KI, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. Lancet Haematol. 2020;7(4):e351-2.
38. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7. doi:10.1016/S1470-2045(20)30096-6
39. Koester V. Coronavirus entering and replicating in a host cell. ChemViews. 2020;5:e1000428. doi:10.1002/chemv.202000018
40. Shalaby NA, Eissa DS, Hassan NM, Al Azhary NM, Saleh AA. Prognostic value of renin gene expression in acute myeloid leukemia. Egypt J Haematol. 2018;43(2):69.
41. Haznedaroglu IC, Beyazit Y. Local bone marrow renin–angiotensin system in primitive, definitive and neoplastic haematopoiesis. Clin Sci. 2013;124(5):307-23.
42. Munro MJ, Wickremesekera AC, Davis PF, Marsh R, Tan ST, Itinteang T. Renin-angiotensin system and cancer: a review. Integr Cancer Sci Ther. 2017;4(2):1-6.
43. Ratajczak MZ, Bujko K, Ciechanowicz A, Sielatycka K, Cymer M, Marlicz W, et al. SARS-CoV-2 entry receptor ACE2 is expressed on very small CD45− precursors of hematopoietic and endothelial cells and in response to virus spike protein activates the Nlrp3 inflammasome. Stem Cell Rev Rep. 2021;17(1):266-77.
44. Cao DY, Saito S, Veiras LC, Okwan-Duodu D, Bernstein EA, Giani JF, et al. Role of angiotensin-converting enzyme in myeloid cell immune responses. Cell Mol Biol Lett. 2020;25:1-2.
45. Seif F, Aazami H, Khoshmirsafa M, Kamali M, Mohsenzadegan M, Pornour M, et al. JAK inhibition as a new treatment strategy for patients with COVID-19. Int Arch Allergy Immunol. 2020;181(6):467-75.
46. Chifotides HT, Bose P, Verstovsek S. Givinostat: an emerging treatment for polycythemia vera. Expert Opin Investig Drugs. 2020;29(6):525-36.
47. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281-92.
48. Lempp FA, Soriaga LB, Montiel-Ruiz M, Benigni F, Noack J, Park YJ, et al. Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. Nature. 2021;598(7880):342-7.
49. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-9. doi:10.1038/s41586-020-2008-3.
50. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):e00127-20.
51. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8.
52. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215-20.
53. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;581(7807):221-4.
54. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensiv Care Med. 2020;46(4):586-90.
55. Li W, Greenough TC, Moore MJ, Vasilieva N, Somasundaran M, Sullivan JL, et al. Efficient replication of severe acute respiratory syndrome coronavirus in mouse cells is limited by murine angiotensin-converting enzyme 2. J Virol. 2004;78(20):11429-33. doi:10.1128/JVI.78.20.11429-11433.2004.
56. Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J. 2005;24(8):1634-43. doi:10.1038/sj.emboj.7600640.
57. McCray Jr PB, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, et al. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J Virol. 2007;81:813-21. doi:10.1128/JVI.02012-06.
58. Moore MJ, Dorfman T, Li W, Wong SK, Li Y, Kuhn JH, et al. Retroviruses pseudotyped with the severe acute respiratory syndrome coronavirus spike protein efficiently infect cells expressing angiotensin-converting enzyme 2. J Virol. 2004;78(19):10628-35. doi:10.1128/JVI.78.19.10628-10635 .2004.
59. Qu XX, Hao P, Song XJ, Jiang SM, Liu YX, Wang PG, et al. Identification of two critical amino acid residues of the severe acute respiratory syndrome coronavirus spike protein for its variation in zoonotic tropism transition via a double substitution strategy. J Biol Chem. 2005;280(33):29588-95. doi:10.1074/jbc.M500662200.
60. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91-8. doi:10.1016/j.jare.2020.03.005
61. Liu J, Wu P, Gao F, Qi J, Kawana-Tachikawa A, Xie J, et al. Novel immunodominant peptide presentation strategy: a featured HLA-A* 2402-restricted cytotoxic T-lymphocyte epitope stabilized by intrachain hydrogen bonds from severe acute respiratory syndrome coronavirus nucleocapsid protein. J Virol. 2010;84(22):11849-57. doi:10.1128/JVI.01464-10.
62. Keicho N, Itoyama S, Kashiwase K, Phi NC, Long HT, Van Ban V, et al. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. Hum Immunol. 2009;70(7):527-31. doi:10.1016/j.humimm.2009.05.006.

63. Chen YM, Liang SY, Shih YP, Chen CY, Lee YM, Chang L, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. J Clin Microbiol. 2006;44(2):359-65. doi:10.1128/JCM.44.2.359-365.2006.
64. Wang SF, Chen KH, Chen M, Li WY, Chen YJ, Tsao CH, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. Virol Immunol. 2011;24(5):421-6. doi:10.1089/vim.2011.0024
65. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7. doi:10.1016/S1470-2045(20)30096-6
66. Fan YY, Huang ZT, Li L, Wu MH, Yu T, Koup RA, et al. Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. Arch Virol. 2009;154(7):1093-9. doi:10.1007/s00705-009-0409-6.
67. Williams AE, Chambers RC. The mercurial nature of neutrophils: still an enigma in ARDS?. Am J Physiol Lung Cell Mol Physiol. 2014;306(3):L217-30. doi:10.1152/ajplung.00311.2013.
68. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin immunopathol. 2017;39(5):529-39. doi:10.1007/s00281-017-0629-x.
69. Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). Virus Res. 2008;133(1):13-9. doi:10.1016/j.virusres.2007.02.014.
70. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. doi:10.1016/S2213-2600(20)30076-X.