

Case Report

Physical Medicine and Rehabilitation Approach of Elderly with Atypical COVID-19 Symptoms

Siti Chandra Widjanantie¹ , Erlina Burhan² , Agus Dwi Susanto²

¹Department of Physical Medicine and Rehabilitation, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

²Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

Correspondent:

Siti Chandra Widjanantie, Department of Physical Medicine and Rehabilitation, Faculty of Medicine, University of Indonesia, Jl. Salemba Raya No.4, Jakarta, Indonesia, sitichandraw@gmail.com

Article info:

Received: November 17, 2023

Received in revised: August 10, 2024

Accepted: August 20, 2024

Published: August 28, 2024

This is an open access article under the CC- BY license

(<https://creativecommons.org/licenses/by/4.0/>)



Cite this as: Widjanantie SC, Burhan E, Susanto AD. Physical Medicine and Rehabilitation Approach of Elderly with Atypical COVID-19 Symptoms. SPMRJ Vol 6 No 2, 184-194

Abstract

Corona Virus Disease 2019 (COVID-19) symptoms and clinical progressiveness may vary from asymptomatic, mild, and moderate symptoms to severe acute respiratory syndrome (SARS). During the pandemic, COVID-19 has affected the older population disproportionately. Elderly patients are prone to have more severe COVID-19 symptoms, and clinical manifestations of COVID-19 in the geriatric population can be atypical and differ from the younger population. Symptoms experienced non-respiratory may include anorexia and gastrointestinal tract symptoms. Sickness anorexia in early illness appears to be a gastrointestinal response to viral infection. We report an 80-year-old male with an atypical presentation of COVID-19. In this case report, we describe an elderly COVID-19 patient with dyspnea, sickness anorexia, and various gastrointestinal symptoms that cause weight loss, anemia, and hypoalbuminemia. We also describe the multidisciplinary aspect of physical medicine and rehabilitation management for the patient. During the treatment, the patient was given mobilization techniques and a regular general endurance exercise for the upper and lower extremities. He was instructed to do the breathing exercises using exercise-guided video once a day, repeated daily, with frequencies adjusted to the patient's tolerance as a part of the pulmonary rehabilitation program. The recording video was registered with the Ministry of Law and Human Rights of the Republic of Indonesia. Functional test evaluation results using 30-second sit-to-stand (30s-STST) improved at discharge, the gastrointestinal symptoms were relieved, and exercises can be continued as a home program. A comprehensive multidisciplinary approach is needed to manage more seniors with COVID-19 due to their uniqueness to maximize their functional abilities.

Keywords: COVID-19, Elderly, Digestive System Disorders, Infectious Disease, Physical Medicine and Rehabilitation

INTRODUCTION

Corona Virus Disease 2019 (COVID-19) symptoms range from asymptomatic, mild symptoms to severe acute respiratory syndrome (SARS). Mild symptoms in more than 80% cases, severe symptoms in about 15% cases, and less than 5% cases experience life-threatening critical conditions. Common clinical manifestations are fever, fatigue, cough, sputum production, shortness of breath, muscle pain, headache, and loss of sense of smell. In addition, gastrointestinal symptoms such as nausea, vomiting, and diarrhea can be found.¹ COVID-19 can cause disorders of various extrapulmonary organs such as the heart, kidney, liver, gastrointestinal, and neurological systems. This damage can occur due to the expression of angiotensin-converting enzyme 2 (ACE2) receptors in these organs.² These organ disorders can be seen in laboratory examinations with abnormalities such as lymphopenia, leukopenia, thrombocytopenia, increased erythrocyte sedimentation rate (ESR) and C-reactive-protein (CRP), advanced cardiac enzymes, decreased albumin, coagulation disorders, and abnormal kidney and liver function.

COVID-19 has led to significant mortality rates among populations deemed vulnerable, particularly the elderly, especially those residing in institutions where maintaining social isolation is challenging during a pandemic. The susceptibility of this demographic is associated with the physiological effects of

aging, which affect the efficiency of the immune system, leading to increased morbidity and mortality from infectious diseases. Elderly patients are known to have a higher risk of severe symptoms and requiring mechanical ventilation^{3,4} Comorbidities in elderly patients, such as diabetes mellitus, hypertension, and cardiovascular disease, are also known to increase the risk of mortality due to COVID-19.^{3,5} We report a case of an elderly patient with COVID-19 with major clinical manifestations in the gastrointestinal tract to further explore the physical medicine and rehabilitation approaches that can be given to improve the functional abilities of COVID-19 patients.

CASE REPORT

An 80-year-old man was admitted to the emergency department with complaints of fever and loss of appetite. The fever was felt to be fluctuating with a temperature of 39.5°C for two weeks. The patient also felt a decrease in appetite and body weakness. He had been seen by a general practitioner and was diagnosed with typhoid fever. The patient received antibiotics and paracetamol. The patient had a nonproductive cough for eight days before hospitalization with no prior history of dyspnea. His condition deteriorated, and he was treated in another hospital. The patient felt weak, had a fluctuating fever, and had no appetite. The patient felt the shortness of breath was worse during activity and decreased while resting. The patient's shortness of breath is not affected by position. The patient lost 5

kilograms of body weight during the illness. The patient was then referred from the previous hospital with the information that the patient was under COVID-19 surveillance and the nasopharyngeal swab results were positive for SARS-CoV-2.

The patient had a history of smoking with a Brinkman index of less than 600. The patient had already quit smoking in the past year. The patient had a history of hypertension controlled with amlodipine 1x5 mg and candesartan 1x8 mg. He also had a history of ischemic stroke ten years ago, which recovered without sequelae. There was no history of allergy, heart disease, tuberculosis, or diabetes mellitus. The patient has a history of cataracts in both eyes and wears spectacles. He had been scheduled for cataract surgery, but the surgery was postponed due to the pandemic.

Before the onset of illness, the patient could perform activities of daily living independently and walk without using assistive devices. The patient exercises regularly by walking in the neighborhood every day. The patient was unemployed and lived in a nursing home, with his room separated from other residents. Since the beginning of the COVID-19 pandemic in Indonesia, the nursing home has restricted visits. However, one nursing home employee was previously confirmed with COVID-19.

On the first day of admission, the patient's blood pressure was 133/68 mmHg, pulse rate was 87 x/min, respiratory rate was 20 x/min, and oxygen saturation was 99% on room air. On physical examination, there

was no increase in jugular venous pressure (JVP). Chest examination revealed symmetrical chest movement during respiration. Vesicular lung sounds were heard on auscultatory review, with no rhonchi or wheezing in either lung. Lower extremity edema was absent. Functional examination revealed chest cavity development of 2-3-4 cm, BORG scale 4, and oxygen saturation of 98-99% during activities in bed. The 30-second sit-to-stand (30s-STST) was inapplicable at the time of the patient's admission to the hospital. The patient could sit up independently by holding on to the bed's railing and sitting upright for 5 minutes without leaning. Radiological abnormalities of the heart or lungs were found on chest X-rays. Electrocardiography (ECG) showed sinus rhythm with infrequent premature atrial complex (PAC). QTc interval was average.

On the first day of treatment, the patient received NaCl 0.9% Intravenous Fluid Drops (IVFD) 42 mL/hour, vitamin C 1 x 400 mg intravenous fluid (IV), azithromycin 1 x 500 mg peroral (PO), oseltamivir 2 x 75 mg PO, hydroxychloroquine 2 x 200 mg PO, amlodipine 1 x 5 mg PO, and candesartan 1 x 8 mg PO. Maintenance therapy was continued until test results were negative and the patient's condition improved.

The physical medicine and rehabilitation program was applied using an exercise guide video entitled "Latihan Pernapasan Pada Lansia" from Persahabatan Hospital's YouTube media channel.⁶ The patient was also given regular rehabilitation

management during inpatient care, starting from a prone position, mobilization, and general endurance exercises, gradually as tolerated. This exercise protocol was registered with the Central Authority Ministry of Law and Human Rights of the Republic of Indonesia (KEMENKUMHAM), with registered number EC00202140691. The patient is sleeping on his back. Hands are placed on the chest and stomach. The patient inhales until his stomach expands and then exhales. The patient inhales while raising his hands, exhales, and lowers his hands. After that, position both hands next to the body, inhale, and exhale in the prone position. The patient is asked to inhale, expand his stomach, and then exhale.

For clinical evaluation, the patient underwent nasopharyngeal and oropharyngeal swab examinations three times with negative results during treatment. By the fifth day of treatment, the patient's cough and shortness of breath had been relieved. The patient's exercise changed to a sitting position. The patient trains to sit relaxed on the edge of the bed, inhales while lifting his knees towards his body, and exhales when he lowers his legs. The patient did it alternately. The next step was for the patient to inhale while straightening the right leg and exhale when they lowered the leg and did it alternately. The patient inhaled while his legs were in a pedaling position, exhaled while lowering his legs, and did it alternately. Furthermore, the patient practiced inhaling, lifting his hands up, and exhaling from his mouth when lowering his

hands. Practice inhaling, stretching his arms out to the sides, exhaling from his mouth, and lowering his hands. Inhale exercise, left hand at the waist and right hand raised upwards from the lateral side, exhale right hand lowered, and do it alternately with the right hand on the waist and the left hand lifted from the lateral side. Place both hands on his waist; inhale; and lift his shoulders; exhale to release from your mouth; inhale while raising his arms straight up; exhale; lower his hands; sit in a sitting or standing position.

However, the patient complained of weakness and loss of appetite, and laboratory results did not improve as the d-dimer level was over 3,000 μg . The rectal swab was performed on the ninth day to clarify the involvement of the gastrointestinal system, which was the patient's dominant complaint during the nine days of treatment. The rectal swab result was negative.

On the 13th day of treatment, there was a decrease in the hemoglobin level to 8.7 g/dL and in the albumin level to 2.8 g/dL. The patient had no history of bleeding, and no fecal hematochezia was found in the stool examination. The patient was transfused with packed red blood cells up to 300 cc to achieve a target hemoglobin of 10 g/dL. The patient received parenteral therapy with 25% albumin 100 cc IV and albumin capsules once daily.

The patient had no complaints on the 15th day of treatment. The patient had no fever, cough, or shortness of breath, and his appetite improved. Oropharyngeal swab

results were negative, and supportive testing for hemoglobin and albumin showed improved results. The patient was discharged from the hospital on the 19th day of treatment. The patient had lost 14 kg since the onset of the illness. After being discharged from the hospital, the patient complained of weakness and was walking with the help of a walker. The follow-up for 30s-STST showed the patient could do eight repetitions in 30 seconds. However, the patient could not continue because he was tired. The Borg scale was 4. The patient could perform independent activities but was limited at a slow pace. The patient was given vitamin C 1 x 50 mg PO, folic acid 1 x 1 tablet PO, clopidogrel 1 x 75 mg PO, atorvastatin 1 x 20 mg PO, cefixime 2 x 200 mg PO, and Albumin 1 x 1 capsule.



Figure 1. Exercise inward (pre-discharge)

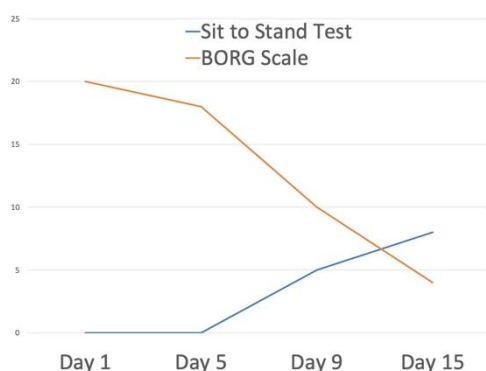


Figure 2. Clinical parameter during pulmonary rehabilitation

DISCUSSION

The patient was confirmed with COVID-19 based on a nasopharyngeal swab at the previous hospital. The results of COVID-19 tests performed when the patient was admitted to Persahabatan Hospital on days 3-5 were negative. The clinical course of COVID-19 infection can vary from asymptomatic to ARDS, requiring intensive care and death.^{1,5} ACE2 receptor expression can be found in various organs, including enterocytes, renal tubular cells, cardiomyocytes, testes, placental trophoblasts, ductal cells, eyes, blood vessels, and respiratory epithelial cells. The expression of ACE2 receptors in these different organs may explain the systemic manifestations of COVID-19.⁷ The systemic manifestations include gastrointestinal symptoms such as anorexia, nausea, vomiting, abdominal pain, and diarrhea. The decrease of appetite, known as sickness anorexia, at early viral infection is the body's immune response.⁸

Gastrointestinal illness in COVID-19 patients can range from 3% to 20%.^{9,10} The finding of SARS-CoV-2 RNA in stool samples from infected patients and the expression of ACE-2 receptors in the gastrointestinal tract suggest that SARS-CoV-2 may replicate in the gastrointestinal tract.¹¹ In COVID-19 patients who experience an increase in the severity of their illness, gastrointestinal symptoms become progressively worse, accompanied by increased liver enzyme levels and coagulation abnormalities. Alteration of upper gastrointestinal symptoms will

interfere with the lower esophageal sphincter; this is related to the crural-diaphragm and worsens primary respiratory muscle function.^{12,13}

By the 9th day of treatment, there was no improvement in the patient's complaints or the results of the supporting tests. The patient still had complaints of weakness, anorexia, and weight loss. Complaints of dyspnea and cough were absent. Laboratory results showed decreased serum albumin and increased CRP and d-dimer. Therefore, it was decided to conduct a PCR examination of an anorectal swab. However, the rectal swab showed negative results. There were different favorable rates based on a systematic review and meta-analysis of the detection profile of SARS-CoV-2 by RT-PCR in different specimen types. Bronchoalveolar lavage fluid is known to have the highest positive rate, followed by rectal swabs and sputum.¹⁴ The patient had a negative result on a rectal swab. This may be due to the time interval of more than 20 days since the onset of symptoms in the patient. Negative consequences may be due to the clearance of viruses in the respiratory and gastrointestinal tracts. A study by Zhou et al. found that the median duration of viral shedding in patients with confirmed COVID-19 was 20 days.¹⁵ However, a survey by Cuicchi et al. found that rectal swab results may remain positive even if the nasopharyngeal swab results are negative.¹⁶ This may reflect clearance of the virus from the respiratory tract. Positive RT-PCR results in rectal swab specimens cannot discriminate between infectious viruses and

noninfectious nucleic acid components.¹⁷ However, SARS-CoV-2 RNA in rectal swab specimens is associated with a more severe course of disease characterized by a higher rate of intensive care unit treatment.¹⁸

Hematologic examination revealed leukocytosis, lymphocytopenia, and neutrophil elevation. In several studies, hematologic abnormalities commonly found in COVID-19 infection are leukopenia, lymphocytopenia, and increased neutrophils.^{1,4} The neutrophil-to-lymphocyte ratio (NLR) can be calculated from the results of the leukocyte count. In some previous studies, NLR has prognostic value in patients with sepsis and malignancies. A study by Fu et al. found that dynamic changes in NLR during treatment can identify patients with a severe disease course. The worsening group of patients had a decreasing number of lymphocyte types and an increasing NLR.¹⁹ The patient was found to have low lymphocytes and a high NLR at the time of admission. During treatment, there was an increase in lymphocyte count, a decrease in NLR, and the patient's clinical improvement.

On day 13 of the treatment, the patient developed hypoalbuminemia. Elderly patients who are hospitalized often have hypoalbuminemia. Hypoalbuminemia can be caused by poor nutritional status, impaired hepatic function, and gastrointestinal losses. In critically ill patients, hypoalbuminemia correlates with increased 30-day mortality, increased risk of complications during treatment, and prolonged hospitalization. The patient

received treatment consisting of a protein intake of 65 g/day and 2x150 cc of milk. For the management of hypoalbuminemia, the patient received 25% albumin 100 cc IV and an albumin capsule once a day. With this management, serum albumin levels increased to 3.1 g/dL at the end of treatment. Serum albumin levels greater than 3.0 g/dL are associated with reduced complications and better clinical outcomes.²⁰

Patients with COVID-19 with poor prognosis can be identified by advanced age, diabetes mellitus, elevated d-dimer, elevated CRP, worsening Sequential Organ Failure Assessment (SOFA) score, and hypoalbuminemia.^{15,20,21} Vitamin C was administered intravenously at a dose of 1x400 mg. In a meta-analysis, vitamin C in a quantity of 1-3 g/day can reduce the length of stay in the ICU by 7.8% and the duration of mechanical ventilation by 18.2%. Vitamin C administration can also reduce lung injury due to oxidative stress induced by the use of mechanical ventilation and reduce mortality in patients treated in the ICU.

At the time of admission, the patient received azithromycin 1x500 mg PO and hydroxychloroquine 2x200 mg PO. Azithromycin is a macrolide antibiotic effective against *Streptococcus pneumoniae* and *Haemophilus influenzae*, which cause respiratory tract infections. It also has anti-inflammatory and immunomodulatory effects. Azithromycin is known to have antiviral effects that can inhibit the replication of rhinovirus, respiratory syncytial virus, and influenza virus.²² The chloroquine group of drugs has long been

used to treat malaria infections and autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Based on in vitro studies, hydroxychloroquine has an antiviral effect against SARS-CoV-2. Hydroxychloroquine is also known to have immunomodulatory effects by reducing the production of cytokines such as IL-1, IL-6, and TNF- α and decreasing autophagy activity in host cells.²³ The combination of azithromycin and hydroxychloroquine therapy has been shown to reduce mortality in hospitalized COVID-19 patients.²⁴ However, another study found that combining the two did not significantly reduce mortality.²⁵ Further studies are needed to determine the efficacy and safety of the combination.

Patients also received oseltamivir 2x75 mg PO in addition to the combination of the two drugs. Oseltamivir is a neuraminidase inhibitor that has been used to treat influenza. Oseltamivir was included in the therapeutic regimen during the early days of the COVID-19 pandemic in Wuhan because it coincided with the influenza season.⁸ However, no studies currently support the efficacy of oseltamivir against SARS-CoV-2. The use of oseltamivir for COVID-19 is presently under clinical investigation.²⁵

The patient has a history of contact with a confirmed COVID-19 patient, a nursing home employee. The patient lives in a nursing home in a room that is separate from the other residents and restricts visitors from outside the nursing home. Transmission of COVID-19 can occur in

patients who are asymptomatic or who do not yet have symptoms. Older adults who live in nursing homes are at a higher risk of infection, mortality, and morbidity during the COVID-19 pandemic. Indoor low-air quality and lack of ventilation in nursing homes are known factors affecting residents' respiratory health and transmission of infections. Data about its infection transmission in nursing homes may be associated with limited personal protective equipment, limited infection prevention protocols, limited staff, older residents, and comorbidities.²⁶

The principle of pulmonary rehabilitation is simple, safe, easy-to-implement exercises so that it can be done anywhere, including during independent isolation at home.²⁷ The role of breathing exercises is to maintain lung development, energy conservation (energy saving) when breathing or doing activities, and fitness during the COVID-19 pandemic to boost physical capability, alleviate psychological stress, and improve the quality of life for individuals recovering from COVID-19.^{27,28} Each rehabilitation plan should consider any concurrent health conditions that might impact a patient's advancement or ability to engage in the program. An effective rehabilitation regimen must incorporate education on COVID-19. Given the novelty of the condition, patients need to be informed about the disease's implications and potential consequences, including post-COVID-19 sequelae post-hospital discharge. Educational initiatives for rehabilitation can be delivered through

various means, such as booklets, videos, telehealth, and direct education, emphasizing the importance of respiratory rehabilitation programs and promoting a healthy lifestyle.²⁸

During the treatment, the patient was instructed to do the breathing exercises using exercise-guided video once a day, repeated daily, and adjusted the frequencies according to patient tolerance. The exercise guide video entitled "Latihan Pernapasan Pada Lansia" from Persahabatan Hospital's YouTube media channel consists of several simple movements so that they can be imitated by the elderly.⁶ The exercises consist of three main movement groups according to body positions: supine, sitting, and standing. The mobilization process means moving safely from the position of the patient lying down to sitting and vice versa, ergonomically maintaining the patient's posture and saving energy so as not to trigger the onset of shortness of breath. This gradual series of moving positions is very beneficial in saving energy expended by the body and preventing muscle injury. Because the elderly population tends to be stiff and their breathing effort is more significant and heavier, they tire quickly.²⁷ In a comfortable seated position, breathing exercises can be performed, whether the patient is long sitting, sitting on the edge of the bed, or in a chair (short sitting) to achieve energy efficiency as the patient moves to perform breathing exercises as part of pulmonary rehabilitation. When lying on the back, the patient coordinates inhaling while moving both arms up and exhaling while

lowering the arms. Breathing exercise in the prone position, known as lung recruitment, is the best position for optimizing the development of lung tissue because the diaphragm moves more lightly and does not fight gravity. At the same time, the entire load of the chest cavity, which is a lot on the front side, is placed on the base as the earth's gravitational force so that breathing movements become greatly alleviated because the heart burdens lung development when lying on your back, is placed by the force of gravity. Pressure mechanics within the lung tissue, specifically within the air sacs (alveoli) in the lungs, are optimized equally across the entire dorsal lung area. Breathing movements also become more dynamic, considering that a series of vertebrae support the dorsal side of the body.²⁷ There is a mild adverse event found in this patient, experiencing mild myalgia in the arms and upper trunk in the first week of exercise. However, he still can deal with it without any episodes of dyspnea after exercise or other respiratory complaints. Breathing exercises for the elderly remain safe and have no adverse events if given depending on the patient's condition and frequently given evaluations.

The sit-to-stand test (STST), commonly known as the 30-second sit-to-stand test (30s-STST), involves an individual sitting on a chair with their back leaning, feet on the floor, and hands crossed on the chest. They are then instructed to repeatedly sit and stand while regulating their breathing for a continuous 30-second period, with the examiner monitoring the

number of sit-stand cycles completed. Each sit-stand cycle is considered one process. The 30s-STST typical result in older people is typically defined as achieving more than 10 cycles in 30 seconds.²⁹ It's important to note that while the sit-to-stand test serves as a clinical monitoring parameter, it is not considered a gold standard. The gold standard for assessing cardiorespiratory endurance involves cardiopulmonary exercise testing (CPET) as a maximum test and the six-minute walk test as a submaximal test.^{27,29} The 30-second sit-to-stand (30s-STST) was inapplicable at the time of the patient's admission to the hospital. However, after undergoing the medical rehabilitation program during inpatient, the functional test results using the 30s-STST improved significantly at discharge, and exercises were continued at home.

CONCLUSION

Elderly patients with COVID-19 with atypical symptoms and no history of typical respiratory symptoms may be associated with inflammation elsewhere, and this needs to be further investigated in elderly patients with a variety of degenerative disorders. Providing a simple medical rehabilitation program that can be implemented in isolation wards for older adults using exercise-guided video is quite helpful. It may improve the functional abilities of the patient.

REFERENCES

1. Yang CY, Lu QB, Liu MJ, Wang YX,

- Zhang AR, Jalali N, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. medRxiv. 2020;2020.02.10.20021675.
2. 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. *Intensive Care Med.* 2020;46(4):586–90.
 3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020;323(16):1574–81.
 4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507–13.
 5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;5(7):802–10.
 6. Persahabatan Hospital. Latihan Pernapasan Pada Lansia [Internet]. 2021. Available from: <https://www.youtube.com/watch?v=UwA2zaSR5oE>
 7. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol.* 2020;16(7).
 8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061–9.
 9. Wan Y, Li J, Shen L, Zou Y, Hou L, Zhu L et al. Enteric involvement in hospitalised patients with COVID-19 outside Wuhan. *lancet Gastroenterol Hepatol.* 2020;5(6):534–5.
 10. Philips CA, Mohan N, Ahamed R, Kumbar S, Rajesh S, George T, et al. One disease, many faces-typical and atypical presentations of SARS-CoV-2 infection-related COVID-19 disease. *World J Clin cases.* 2020;8(18):3956–70.
 11. Wong SH, Lui RNS, Sung JY. Covid-19 and the digestive system. *J Gastroenterol Hepatol.* 2020;35(5):744–8.
 12. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol.* 2020;115(5):766–73.
 13. Widjanantie SC, Syam AF, Nurdwinuringtyas N, Susanto AD, Hidayat R, Kekalih A, et al. Effects of Modified Diaphragmatic Training on Gastroesophageal Reflux Disease Questionnaire Score, Diaphragmatic Excursion, and Maximum Inspiratory Pressure in Adults with Gastroesophageal Reflux Disease After COVID-19: A Single-Blinded Randomized Cont. *Acta Med Indones.* 2023;55(3):269–76.
 14. Bwire GM, Majigo M V., Njiro BJ, Mawazo A. Detection profile of SARS-CoV-2 using RT-PCR in different types of clinical specimens: A systematic review and meta-analysis. *J Med Virol.* 2021;93(2):719–25.
 15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054–62.
 16. Cuicchi D, Lazzarotto T, Poggioli G. Fecal-oral transmission of SARS-CoV-2: review of laboratory-confirmed virus in gastrointestinal

- system. *Int J Colorectal Dis.* 2021;36(3):437–44.
17. Barth RE, De Regt MJA. Persistence of viral RNA in stool samples from patients recovering from COVID-19. *BMJ.* 2020;369.
18. Lin W, Xie Z, Li Y, Li L, Wen C, Cao Y, et al. Association between detectable SARS-CoV-2 RNA in anal swabs and disease severity in patients with coronavirus disease 2019. *J Med Virol.* 2021;93(2):794.
19. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. *J Infect.* 2019;78(5):339–48.
20. Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, et al. Is Albumin Predictor of Mortality in COVID-19? *Antioxid Redox Signal.* 2021;35(2):139–42.
21. Rod JE, Oviedo-Trespalacios O, Cortes-Ramirez J. A brief review of the risk factors for COVID-19 severity. *Rev Saude Publica.* 2020;54.
22. Tran DH, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with the virus internalization process. *J Antibiot (Tokyo).* 2019;72(10):759–68.
23. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020;71(15):732–9.
24. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA.* 2020;323(24):2493–502.
25. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;323(18):1824–36.
26. Fallon A, Dukelow T, Kennelly SP, O'Neill D. COVID-19 in Nursing Homes. *QJM An Int J Med.* 2020;113(6):391–2.
27. Widjanantie SC. Pandemi COVID-19 & Rehabilitasi Respirasi: Rekam Jejakku Semasa Pandemi. Malang: Litera Media Tama; 2022.
28. Hasanudin H, Sukartini T, Makhfudli M, Rosyid AN, Revita NCT, Aini HN. The Effectiveness of Pulmonary Rehabilitation on Pulmonary Function among Adults Patients of COVID-19 Survivors: A Systematic Review. *J Respirasi.* 2022;8(1):15.
29. Zanini A, Crisafulli E, D'andria M, Gregorini C, Cherubino F, Zampogna E, et al. A minimum clinically important difference in 30-s sit-to-stand test after pulmonary rehabilitation in subjects with COPD. *Respir Care.* 2019;64(10):1261–9.