Ischemic Stroke in Corona Virus Disease 2019 with Vascular Cognitive Impairment and Pulmonary Tuberculosis - A Case Report

Gloria Wongkar[1], Gerard Juswanto[2], Lidia Rombeallo[3], and Titi Mutiara[3], Irwan Tansil[4], Firmansya[5]

[1]General Practitioners of Biak Indonesia General Hospital, Papua Province, Indonesia, 98515
[2]Neurologists of Biak Indonesia General Hospital, Papua Province, Indonesia, 98515
[3]Internist of Biak Indonesia General Hospital, Papua Province, Indonesia, 98515
[4]Radiologists of Biak Indonesia General Hospital, Papua Province, Indonesia, 98515
[5]Anesthesiologists of Biak Indonesia General Hospital, Papua Province, Indonesia, 98515

E-mail: g.wongkar08@gmail.com; gerardjuswanto@gmail.com; rombeallolidia@yahoo.com; titimutiara72@gmail.com; irwantansil@yahoo.com; dr.firmansya@gmail.com

*Corresponding author details: Gloria Wongkar; g.wongkar08@gmail.com

ABSTRACT

Background: COVID-19 is a global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus was declared by the World Health Organization (WHO). Many other conditions, including neurological conditions, may complicate COVID-19. COVID-19 is known to increase the risk of ischemic stroke due to COVID-19-associated coagulation (CAC) and the neurotropism of SARS-CoV-2. Tuberculosis is a chronic disease that can cause stroke with vasculitis and hypoxia pathways. Tuberculosis also lowers the immune system, making it easier to get infected by SARS-CoV-2. This case aimed to report a case of recurrent ischemic stroke in COVID-19 with VCI and Pulmonary TB in Biak, Papua, Indonesia. *Case:* A man-69 years old with vascular cognitive impairment because of their first ischemic stroke currently comes with recurrent ischemic stroke with right hemiparesis and right central facial nerve paralysis. The patient has a history of pulmonary TB on treatment. In the course of the patient's illness, the patient has worsening consciousness and oxygen saturation; CT Thorax shows right collapse pneumothorax bronchopneumonia with a positive SARS-CoV-2 PCR test. *Conclusion:* Ischemic stroke can be present along with COVID-19, especially in severe conditions with the existence of pulmonary TB coinfection.

Keywords: COVID-19; Ischemic stroke; pulmonary tuberculosis; SARS-CoV-2

INTRODUCTION

Since December 2019, a new virus that has emerged in the city of Wuhan, China, known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged and caused severe respiratory infections, namely coronavirus disease 2019 [1]. SARS-CoV-2 is transmitted through droplets from infected people or indirect contact [2–4]. SARS-CoV-2 spread globally until, on March 11, 2020, COVID-19 was declared a global pandemic by the World Health Organization (WHO). WHO reported more than 190 million confirmed cases of COVID-19, including 4,093,145 deaths in the world as of July 19, 2021. have recovered, and 76,200 patients have died [5].

The definition of ischemic stroke, according to the American Stroke Association (ASA), is an episode of neurological dysfunction caused by blockage of blood vessels that occurs in a focal area of the brain, spinal cord, or retina [6].

Early symptoms of COVID-19 are reported as fever, cough, shortness of breath, and hypoxia. Severe with angiotensin-converting enzyme 2 (ACE2) as the primary receptor [7–9]. COVID-19 has neuroinvasive capabilities and shows neurological manifestations, including cerebrovascular events, headaches, and vestibular and cognitive disorders [10–13]. The invasion of SARS-CoV-2 into the human body causes an increase in the immune system, with the effect of increasing the permeability of the blood-brain barrier (BBB) so that SARS-CoV-2 can attack the central nervous system (CNS) via transcellular, paracellular, and axonal retrograde transport through the sensory and olfactory nerves (lamina cribriform and olfactory bulb) [14–17]. The combination of cytokine storms that cause coagulation and thrombosis (Covid-19 Associated Coagulation (CAC)) and viral neurotropism (the ability of the virus to attack and survive in SSP) [14,18].

A retrospective study by Li Y. et al. (2020) reported that ischemic stroke is the most common stroke incident in COVID-19 patients; neurological symptoms occur in around 36% of patients suffering from COVID-19. 22 This case aims to report cases of ischemic stroke in COVID-19-positive patients in Biak, Papua, Indonesia.

CASE REPORT

A 69-year-old man was taken to the emergency room at Biak Regional Hospital with the main complaint of decreased consciousness for 2 hours at SMRS. Neurological examination revealed decreased consciousness, restlessness, vital signs GCS E3M4V suspected of aphasia, BP 156/89mmHg, pulse (HR): 89x/minute, respiratory rate (RR): 22x/minute, body temperature (T): 380C, and blood oxygen saturation (SpO2): 90%. Physical examination lateralized to the right, right central facial nerve paresis, right physiological reflex increased, right pathological reflex (+). Previous medical history includes ischemic stroke with sequelae of VCI and a history of pulmonary TB. The supporting results of plain head MSCT showed cerebral infarction in the left centrum semi-ovale, left internal capsule, and left corona radiata (Figure 1). Thorax X-ray photos show a picture of active TB. Non-reactive COVID-19 antigen, non-reactive PITC, outpatient management with a specialist in internal medicine with complaints of shortness of breath and rough wet crackles in both lungs. Category 1 (1x3 FDC tablets) is the initial phase in treating pulmonary TB.
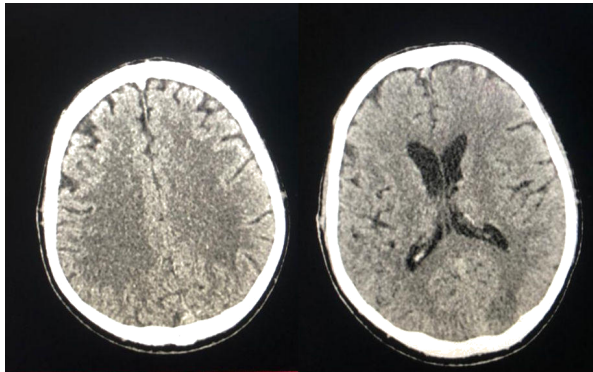

FIGURE 1: MSCT Plain head.

The course of the patient's illness became increasingly breathless, and consciousness decreased; GCS E2M4V suspected aphasia, BP 110/70mmHg, HR: 125x/minute, RR: 36x/minute, T: 38.80C, SpO2: 60%. The results of a CT scan of the thorax showed that the patient had bronchopneumonia collapsing right pneumothorax with marked consolidation at the right pulmonary apex, which indicated the presence of active pulmonary TB (Figure 2), RT-PCR was reactive (CT value 16). Abnormalities in laboratory results were increased creatine levels (1.2 mg/dl) and liver function (SGOT=47 U/L, SGPT= 61 U/L). Management of the patient is given oxygen 8-10 liters per minute (lpm) NRM, head raised 30 degrees, IVFD Ringer lactate 20 drops per minute, Paracetamol injection 1g/8 hours IV, Clopidogrel 75mg/24 hours po, Aspilet 80mg/24 hours po,

Vitamins B1, B6, B12 1 tab/24 hours po, Citicolin injection 500mg/12 hours IV, Ceftriaxone injection 2gram/24 hours IV, Omeprazole injection 40mg/12 hours IV, Ondancetron injection 8mg/8 hours IV, OAT po, patient installed NGT and DC.
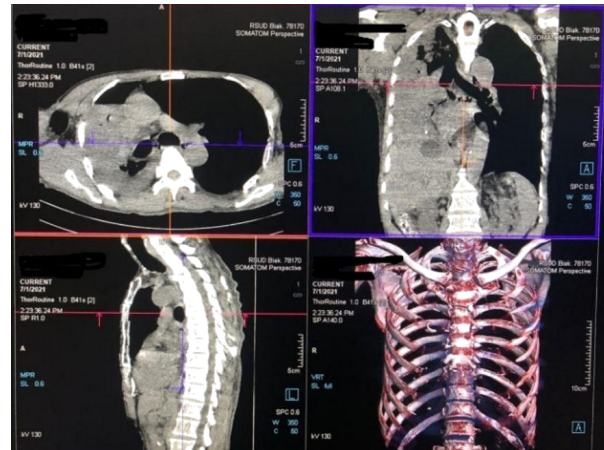

FIGURE 2: Plain Thoracic CT Scan.

On the third day of treatment, the patient was transferred to the COVID-19 isolation ICU room and treated by an Internal Medicine specialist and an Anesthesia specialist. Vital signs GCS E3M4V suspected aphasia, BP 125/75mmHg, HR: 106x/minute, RR: 25x/minute, T: 380C, SpO2: 86% NRM 3 pm, which was then intubated and installed on a ventilator.

Additional management of Remdesivir Drip IV injection (Day 1= 200mg/24 hours IV, Days 2-5= 100mg/24 hours IV), Resfar Drip 1 vial/24 hours IV, Levofloxacin injection 750mg/24 hours IV, Dexamethasone injection 5mg/12 IV hours, Meropenem injection 1gram/8 hours IV, OBH IIC/8 hours po, Vitazet 1 tab/12 hours po, Curcuma 1 tab/24 hours po.

On the fourth to the eighth day of treatment, the patient's condition improved, but the shortness of breath worsened, and the crackles in both lungs became more transparent, thicker, and rougher. On the eighth day of treatment, the patient experienced a worsening decrease in consciousness to sopor from previous apathy, vital signs GCS E1M2V suspected aphasia, BP 80/50mmHg, HR: 140x/minute, RR: 20x/minute, SpO2: 85% then given Norepinephrine 0.1 mcg /body weight/min. However, the patient's condition continued to worsen, and he experienced heart failure Cardiopulmonary resuscitation with Epinephrine injection, the patient died on the ninth day of treatment.

TABLE 1: Complete Blood Examination Results.

Component	Date 6/30	Parameters
HB	14.7	Gr/Dl
RBC	4.6	Million/mm3
HCT	42	%
Leukocytes	7,200	/mm3

Component	Date 6/30	Parameters
Differential Count		
- Basophils	0	%
- Eosinophils	2	%
- Bands	0	%
- Segment	67	%
- Lymphocytes	22	%
- Monocyte	9	%
Platelets	286	103/mm3

TABLE 2: Blood Chemistry Test Results.

Component	Date 6/30	1/7	Parameter
GDP	75	115	Mg/dl
Total cholesterol	152	167	Mg/dl
Triglycerides	69	68	Mg/dl
Creatinine	1,2	1.3	Mg/dl
Gout		6,8	Mg/dl
Albumin	5.9	4.5	Gr/L
SGOT	47	51	U/L
SGPT	61	56	U/L

DISCUSSION

This case report is the first case report to discuss ischemic stroke in a COVID-19-positive patient in Papua, Indonesia. This patient has a history of pulmonary TB, ischemic stroke, and vascular cognitive impairment (VCI) with impaired concentration or attention previously. Decreased consciousness is one of the manifestations of COVID-19 in the field of neurology; previous research shows that 2.4-14.8% of COVID-19 patients experience decreased consciousness, which is related to the severity of the COVID-19 infection [19]. In Small Vessel Disease (SVD), disorders are associated with lacunar infarctions in the subcortical region's white matter and gray matter, which spread evenly and provide a poor picture. Microvascular fibrosis and thickening of the basement membrane, which then causes narrowing of the arterial lumen due to loss of smooth muscle cells. Apart from that, the perivascular space also widens, and plasma protein leakage occurs. These changes can cause blood vessel occlusion, microaneurysms, and fibrinoid necrosis of the blood vessel walls, resulting in ischemic stroke with impaired cognition [20,21]. The patient, in this case, had impaired attention and concentration, making it difficult to comply with the COVID-19 prevention protocol. This was accompanied by impaired immunity due to suboptimal rest time, the initial entry point for infection.

Tuberculosis is associated with an increased risk of ischemic stroke due to vasculitis or intimal proliferation, leading to thrombosis in the brain. The vasculitis is accompanied by thrombosis and infarction of the corticomeningeal blood vessels that cross the basement membrane or are in the brain parenchyma.

Infection with Mycobacterium tuberculosis causes activation of a persistent inflammatory response that initiates a cascade of cytokines and chemokines. The inflammatory response has been established to be of pathogenic relevance in the relationship between infection and atherosclerosis. It may be related to endothelial dysfunction elicited by bacterial endotoxin and cytokine action [22–26]. Sheu JJ et al. found that 6.0% of tuberculosis patients experience an ischemic stroke, in which case these patients have a greater likelihood of experiencing an ischemic stroke over 3 years than the general population [25].

The pathophysiology of ischemic stroke in COVID-19 is related to the host immune system, SARS-CoV-2 neurotropism, and the indirect influence of COVID-19 infection on stroke risk factors. The cytopathic effects of SARS-CoV-2 and dysregulation of the immune system can cause severe inflammation, including a cytokine storm leading to CAC and thrombosis, especially in patients with a history of chronic immune-mediated inflammation, such as tuberculosis, hypertension, VCI, stroke, diabetes mellitus, and metabolic syndrome [27–30]. Elevated coagulation factors (D-dimer and fibrinogen) and increased inflammatory markers (C-reactive protein) result from the CAC process and thrombosis [10]. Vasculitis of the central nervous system can also contribute to the pathophysiology of stroke ischemia in COVID-19 [31,32]. Hanafi R et al. (2020) reported imaging of "patchy/punctate enhancement" vasculitis on cerebral MRI [31].

SARS-CoV-2 can bind to toll-like receptors and cause activation of pro-inflammatory cytokines (IL-1). Activation of IL-1 will induce a biochemical cascade and activate other pro-inflammatory cytokines (IL-6, IL-2, IL-7, IFN-γ, granulocyte-colony stimulating factor, monocyte chemo-attractant protein 1, tumor necrosis factor-α (TNF-α), and macrophage inflammatory proteins [10,33,34]. This systemic inflammation is associated with acute cerebral ischemia [10,35].

The SARS-CoV-2 spike glycoprotein can bind to the ACE2 receptor (the virus enters cells and proliferates) with the help of transmembrane serine 2 protease (TMPRSS2) and causes down-regulation of ACE2 and invades neurons, glial cells, and vascular endothelium. This excessive binding of ACE2 receptors reduces the activity of the alternative renin-angiotensin-system (RAS) axis, which causes vasoconstrictive effects on cerebral blood vessels (imbalance in vasodilation), neuroinflammation, increased oxidative stress, and triggers fibrosis and thrombosis processes that impact the brain parenchyma. And the occurrence of stroke [10,36,37].

QManagement of ischemic stroke in COVID-19 is the same as for ischemic stroke in general, namely, with reperfusion as a priority. The use of anticoagulants or antiplatelets can be given to reduce the incidence of thromboembolism due to the high risk of prothrombotic disorders [36,38].

The outcomes of patients with stroke and COVID-19 are worse if multi-organ failure or pulmonary disorders occur [37,39,40]. The patient in this case report also showed signs of severe infection characterized by rapid deterioration, the presence of liver and kidney failure, and the occurrence of vascular thrombosis, including stroke. he was more likely to undergo acute respiratory distress syndrome (ARDS), mechanical ventilation support, and intensive care. [41].

Initial intensive management of hypoxemia includes conventional oxygen therapy, high-flow nasal cannula (HFNC) oxygen, and non-invasive ventilation (NIV); lung-protective ventilation with low tidal volume and high pressure is recommended for patients requiring invasive mechanical ventilation. Severe COVID-19 patients usually show a respiratory rate of 30 breaths per minute, oxygen saturation ≤93%, lung infiltration >50%, and are at high risk of clinical deterioration and ARDS. 52,53 The target of ARDS treatment is to achieve a minimum oxygen saturation between 92-96% [42].

Patient management is by the Revised COVID-19 Management Protocol Guidelines; monitoring is carried out in the isolation room by closely monitoring vital signs, calorie intake, electrolyte control, hydration, and oxygen status; blood laboratory monitoring; and serial chest radiographs. There is dysregulation in pulmonary perfusion in COVID-19, loss of vasoconstriction in hypoxic lungs, excessive pulmonary vasoconstriction, and microthrombosis or macrothrombosis [43,44]. Pulmonary microthrombosis and endothelial damage resulting in V/Q (ventilation/perfusion) mismatch, hypoxemia, and vasodilation.57-,58,59 NIV, such as BIPAP or HFNC, is recommended as initial therapy in patients with respiratory failure due to COVID-19 with 3 essential steps: (1) use HFNC or NIV or extensive pulmonary effusion. (2) limiting fluid resuscitation (3) Positioning the conscious patient in an awake prone position [45,46]. The use of mechanical ventilation aims to maintain lung protection in ARDS patients, with a target tidal volume of 4-8 ml/kg bb and plateau pressure <30 cmH20and driving pressure <15 cmH20 [46,47].

The necessary pharmacological therapy in treating COVID-19 is antivirals; based on the revised protocol, the antivirals used are Favipiravir (loading dose 1600 mg/12 hours/oral on day 1 and then 2x600 mg on days 2-5) and Remdesivir (drip 200 mg IV continued 1x100mg IV drip days 2-5 or days 2-10). Antiviral therapy was carried out in the patient in the case according to the latest revised protocol [48,49].

This patient experienced a stroke with various complications due to respiratory problems and inflammatory processes due to pulmonary TB and Covid 19. This contributes to the high mortality rate in patients [50].

Our report has several limitations. We have limited access to advanced diagnostic tools and intensive equipment, so we have limited evidence of another organ involvement that could affect this patient's outcome. For example, blood gas analysis is used to see signs of acidosis or D-Dimer. CRP and NLR value tests are used as diagnostic tools and biochemical markers of severity related to mortality and case fatality rate [50,51].

CONCLUSION

Ischemic stroke can be found simultaneously with SARS-CoV-2 (COVID-19) infection; management becomes increasingly difficult due to pulmonary TB coinfection so that it develops into ARDS, which results in increasingly fatal infections, but it is a challenge, managing COVID-19 is difficult during the pandemic This.

AUTHOR'S STATEMENT
All authors have read and approved the abstract and text above.

REFERENCES

[1]   Di Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, et al. Coronavirus Diseases (COVID-19) Current Status and Future Perspectives: A Narrative Review. Int J Environ Res Public Health 2020;17:2690. https://doi.org/10.3390/ijerph17082690.

[2]   Lotfi M, Hamblin MR, Rezaei N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. Clinica Chimica Acta 2020;508:254–66. https://doi.org/10.1016/j.cca.2020.05.044.

[3]   Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. JAMA Neurol 2020;77:1366. https://doi.org/10.1001/jamaneurol.2020.2730.

[4]   Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Emergence, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91–8. https://doi.org/10.1016/j.jare.2020.03.005.

[5]   World Health Organization. WHO COVID-19 Case definition. Updated in Public Health Surveillance for COVID-19 2020:1.

[6]   Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ (Buddy), Culebras A, et al. An Updated Definition of Stroke for the 21st Century. Stroke 2013;44:2064–89. https://doi.org/10.1161/STR.0b013e318296aeca.

[7]   Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clinical Immunology 2020;215:108427. https://doi.org/10.1016/j.clim.2020.108427.

[8]   Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433.

[9] Fu B, Chen Y, Li P. 2019 novel coronavirus disease with secondary ischemic stroke: two case reports. BMC Neurol 2021;21:4. https://doi.org/10.1186/s12883-020-02033-3.

[10] Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, et al. Coronavirus Disease 2019 and Stroke: Clinical Manifestations and Pathophysiological Insights. Journal of Stroke and Cerebrovascular Diseases 2020;29:104941. https://doi.org/10.1016/j.jstrokecerebrovas dis.2020.104941.

[11] Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther 2020;26:499–501. https://doi.org/10.1111/cns.13372.

[12] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683. https://doi.org/10.1001/jamaneurol.2020.1 127.

[13] Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg 2020;194:105921. https://doi.org/10.1016/j.clineuro.2020.105 921.

[14] Pinzon R, Zalukhu M. Nyeri Sentral Pasca Stroke. Kedokteran Indonesia 2016;NO. 10 TAH:560–2.

[15] Wang H-Y, Li X-L, Yan Z-R, Sun X-P, Han J, Zhang B-W. Potential neurological symptoms of COVID-19. Ther Adv Neurol Disord 2020; 13:175628642091783. https://doi.org/10.1177/1756286420917830.

[16] Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. Acta Neurol Scand 2020;142:14–22. https://doi.org/10.1111/ane.13266.

[17] 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. The Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[18] Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. Front Cell Neurosci 2018;12. https://doi.org/10.3389/fncel.2018.00386.

[19] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–90. https://doi.org/10.1001/jamaneurol.2020.1 127.

[20] Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA 2019;322:1589. https://doi.org/10.1001/jama.2019.4782.

[21] Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. American Journal of Psychiatry 2015;172:323–34. https://doi.org/10.1176/appi.ajp.2014.1407 0878.

[22] Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5:279–84. https://doi.org/10.1136/svn-2020-000431.

[23] Bahr NC, Marais S, Caws M, van Crevel R, Wilkinson RJ, Tyagi JS, et al. GeneXpert MTB/Rif to Diagnose Tuberculous Meningitis: Perhaps the First Test but not the Last. Clinical Infectious Diseases 2016;62:1133–5. https://doi.org/10.1093/cid/ciw083.

[24] Misra UK, Kalita J, Maurya PK. Stroke in tuberculous meningitis. J Neurol Sci 2011;303:22–30. https://doi.org/10.1016/j.jns.2010.12.015.

[25] Sheu J-J, Chiou H-Y, Kang J-H, Chen Y-H, Lin H-C. Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke 2010;41:244–9. https://doi.org/10.1161/STROKEAHA.109.5 67735.

[26] Algood HMS, Chan J, Flynn JL. Chemokines and tuberculosis. Cytokine Growth Factor Rev 2003;14:467–77. https://doi.org/10.1016/S1359-6101(03)00054-6.

[27] Libby P, Egan D, Skarlatos S. Roles of Infectious Agents in Atherosclerosis and Restenosis. Circulation 1997;96:4095–103. https://doi.org/10.1161/01.CIR.96.11.4095.

[28] Libby P, Ridker PM, Maseri A. Inflammation and Atherosclerosis. Circulation 2002;105:1135–43. https://doi.org/10.1161/hc0902.104353.

[29] Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nat Rev Immunol 2020;20:271–2. https://doi.org/10.1038/s41577-020-0312-7.

[30] Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan H, et al. Coronavirus Disease 2019: Tinjauan Literatur Terkini. Jurnal Penyakit Dalam Indonesia 2020;7:45. https://doi.org/10.7454/jpdi.v7i1.415.

[31] Hanafi R, Roger P-A, Perin B, Kuchcinski G, Deleval N, Dallery F, et al. COVID-19 Neurologic Complication with CNS Vasculitis-Like Pattern. American Journal of Neuroradiology 2020;41:1384–7. https://doi.org/10.3174/ajnr.A6651.

[32] Almashat SA. Vasculitis in COVID-19: A Literature Review. J Vasc 2020;6:1–5.

[33] Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci 2019;20:3328. https://doi.org/10.3390/ijms20133328.

[34] Shimizu H, Sakimoto T, Yamagami S. Pro-inflammatory role of NLRP3 inflammasome in experimental sterile corneal inflammation. Sci Rep 2019;9:9596. https://doi.org/10.1038/s41598-019-46116-9.

[35] Arroja MMC, Reid E, McCabe C. Therapeutic potential of the renin angiotensin system in ischaemic stroke. Exp Transl Stroke Med 2016;8:8. https://doi.org/10.1186/s13231-016-0022-1.

[36] Hassett C, Gedansky A, Mays M, Uchino K. Acute ischemic stroke and COVID-19. Cleve Clin J Med 2020. https://doi.org/10.3949/ccjm.87a.ccc042.

[37] Tiwari A, Berekashvili K, Vulkanov V, Agarwal S, Khaneja A, Turkel-Parella D, et al. Etiologic Subtypes of Ischemic Stroke in SARS-CoV-2 Patients in a Cohort of New York City Hospitals. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.01004.

[38] Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020;91:889–91. https://doi.org/10.1136/jnnp-2020-323586.

[39] Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected Code Stroke. Stroke 2020;51:1891–5. https://doi.org/10.1161/STROKEAHA.120.029838.

[40] Yang B, Wang T, Chen J, Chen Y, Wang Y, Gao P, et al. Impact of the COVID-19 pandemic on the process and outcome of thrombectomy for acute ischemic stroke. J Neurointerv Surg 2020;12:664–8. https://doi.org/10.1136/neurintsurg-2020-016177.

[41] Tsivgoulis G, Katsanos AH, Ornello R, Sacco S. Ischemic Stroke Epidemiology During the COVID-19 Pandemic. Stroke 2020;51:1924–6. https://doi.org/10.1161/STROKEAHA.120.030791.

[42] Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med 2021;26:107–8. https://doi.org/10.1136/bmjebm-2020-111536.

[43] Camporota L, Vasques F, Sanderson B, Barrett NA, Gattinoni L. Identification of pathophysiological patterns for triage and respiratory support in COVID-19. Lancet Respir Med 2020;8:752–4. https://doi.org/10.1016/S2213-2600(20)30279-4.

[44] Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Critical Care and Resuscitation 2020;22:95–7. https://doi.org/10.51893/2020.2.pov2.

[45] Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854–87. https://doi.org/10.1007/s00134-020-06022-5.

[46] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the Sp o 2 /F io 2 Ratio and the Pa o 2 /F io 2 Ratio in Patients With Acute Lung Injury or ARDS. Chest 2007;132:410–7. https://doi.org/10.1378/chest.07-0617.

[47] Hajjar LA, Costa IBS da S, Rizk SI, Biselli B, Gomes BR, Bittar CS, et al. Intensive care management of patients with COVID-19: a practical approach. Ann Intensive Care 2021;11. https://doi.org/10.1186/s13613-021-00820-w.

[48] Hajjar LA, Costa IBS da S, Rizk SI, Biselli B, Gomes BR, Bittar CS, et al. Intensive care management of patients with COVID-19: a practical approach. Ann Intensive Care 2021;11:36. https://doi.org/10.1186/s13613-021-00820-w.

[49] Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Crit Care 2020;24:559. https://doi.org/10.1186/s13054-020-03273-y.

[50] Zhan L, Liu Y, Cheng Y, Guo W, Yang J. Predictive value of neutrophil/lymphocyte ratio (NLR) on cardiovascular events in patients with COVID-19. Int J Gen Med 2021;14:3899–907. https://doi.org/10.2147/IJGM.S317380.

[51] Huang H, Shan K, Liu J, Tao X, Periyasamy S. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Bioorg Chem 2020; 103:104230.