4th Riau Medical Scientific and Expo 2022
Volume 2022
http://dx.doi.org/10.11594/nstp.2022.2820

NST Proceedings
OPEN ACCESS

Conference Paper

Correlation Between C-Reactive Protein (CRP) and Lactate Dehydrogenase (LDH) Levels with Severity and Predicting Outcome of Confirmed Covid-19 at Arifin Achmad Hospital, Riau Province

Adrianison[1], Indra Yovi[1], Jemmy Fandri[2]*

[1]Staff of Pulmonology and Respiratory Medicine Department, Faculty of Medicine, University of Riau, Arifin Achmad Hospital, Pekanbaru, Indonesia
[2]Resident of Pulmonology and Respiratory Medicine Department, Faculty of Medicine, University of Riau, Arifin Achmad Hospital, Pekanbaru, Indonesia

Corresponding author:
E-mail:
jemmyfandri@gmail.com

ABSTRACT

Coronavirus Disease 19 (COVID-19) triggers a series of inflammatory processes. The inflammatory process damages the hematopoiesis system, especially the bone marrow, releasing white blood cells and stimulating the liver to secrete acute phase proteins such as ferritin, C-Reactive Protein (CRP), and Lactate Dehydrogenase (LDH). Laboratory tests including CRP and LDH can determine the severity of COVID-19. This study has the purpose to investigate the correlation between LDH and CRP with the severity of confirmed COVID-19 patients and predicting the outcome. This study used a cross-sectional design to determine whether CRP and LDH were able to predict mortality in confirmed COVID-19 patients about illness severity who were hospitalized from April 2020 - July 2021 at Arifin Achmad Hospital Pekanbaru. This study included 522 patients, of which 73 patients (14.00%) died and 449 patients (86.00%) experienced improvement during treatment. The mean LDH and CRP levels in this study were 293.47 ± 192.64 u/L and 55.48 ± 79.03 u/L, respectively. The area under the curve (AUC) ROC for patient outcomes on LDH and CRP examinations was 0.74 and 0.80 with cut-off levels of LDH and CRP to predict mortality in COVID-19 patients of 297 (sensitivity, specificity, PPV, NPV = 60.2%, 53.9%, 17.5%, and 89.3%) and 52 (sensitivity, specificity, PPV, NPV= 63.0%, 78.1%, respectively, 31.9%, and 92.8%) with p-values for all results <0.001. CRP and LDH testing can be used to predict death, but in this study, CRP has an advantage in predicting death.

Keywords: COVID-19, C-Reactive protein, lactate dehydrogenase, severity

Introduction

SARS-CoV-2 is a distinct version of the Coronavirus, a pathogen that affects the respiratory system and is thought to be the cause of SARS. On December 31, 2019, a new virus was discovered for the first time in China (Fang et al., 2020; Di Gennaro et al., 2020; WHO, 2020). The investigation of lower respiratory tract isolate revealed the identification of a novel form of Coronavirus, and the World Health Organization (WHO) has named it Coronavirus Disease 2019 (COVID-19). WHO declared COVID-19 as a pandemic on March 11, 2020 (Salehi et al., 2020). The incidents of this new disease continue to increase over time. COVID-19 treatment relies heavily on laboratory tests. We can establish the prognosis by starting with screening, diagnosis, therapy monitoring, and treatment (Channappanavar & Perlman, 2017; Chua et al., 2020; Gorbalenya, 2020).

The inflammatory process disrupts the hematopoiesis system, especially the bone marrow, cause releasing of white blood cells and stimulation of the liver to produce acute phase proteins such as Lactate Dehydrogenase (LDH), ferritin, and C-Reactive Protein (CRP). The symptoms

How to cite:
Adrianison, Yovi, I., & Fandri, J. (2022). Correlation between C-Reactive Protein (CRP) and Lactate Dehydrogenase (LDH) levels with severity and predicting outcome of confirmed covid-19 at Arifin Achmad Hospital, Riau Province. *4th Riau Medical Scientific and Expo 2022*. NST Proceedings. pages 97-102. doi: 10.11594/ nstp.2022.2820

severity of COVID-19 individuals range from asymptomatic to life-threatening. One of the most common cause of death in COVID-19 patients is Acute respiratory distress syndrome (ARDS) (Lingeswaran et al., 2020; Gaebler et al., 2021). C-Reactive Protein (CRP), which is produced primarily in the liver, is an acute-phase protein in response to the inflammatory cytokine Interleukin-6 (IL-6). In pneumonia, it is a measure of inflammation that must be used to predict disease severity (Gorbalenya, 2020; Centers for Disease Control and Prevention, 2020; Ali et al., 2020).

The enzyme lactate dehydrogenase (LDH) converts pyruvate into lactic acid, which is necessary for energy production. The highest concentrations of the LDH enzyme are found in the lungs, liver, heart, kidneys, muscles, and blood cells (Pons et al., 2021; Huang et al., 2020). According to the researchers, in COVID-19 patients elevated LDH levels are associated with the body's response to infection. Cytokine production promotes the activity of inflammatory mediators and lung fibrosis. LDH levels of more than 500 u/L have been found in H1N1 influenza cases and are associated with more severe morbidity. LDH is the primary enzyme involved in anaerobic respiration, and its activity is increased when the cell is exposed to hypoxia. Cells require oxygen for a variety of reasons, including energy generation, protection from external substances, and task performance. Cell hypoxia is a complex reaction that affects the process of gene transmission and expression in several ways (Wang et al., 2021; Del Valle et al., 2020).

Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), ferritin, D-Dimer, and Interleukin-6 are all laboratory markers that are highly predictive severity of COVID-19 (Centers for Disease Control and Prevention, 2019). Research by Tan et al in 2020 found that CRP increased > 23.5% in critically ill COVID-19 patients (Tan et al., 2020). Mueller's cohort study in Wuhan in 2020 found an increase in CRP levels > 41.8 mg/dl in patients with a severe degree of COVID-19 (Mueller et al., 2020). Henry et al research found that increased LDH levels were associated with a 6-fold chance of progression of COVID-19 to severe degrees and a 16-fold increase in death in COVID-19 patients (Henry et al., 2020). Research by Poggiali et al explained that LDH and CRP concentrations were related to PaO2/FiO2 levels which were associated with markers of inflammation, tissue damage, and markers of infection (Pogiali et al., 2020). A study by Tjahyadi et al. (2020) in Malang 2020 found that LDH and CRP could early predict the incidence of respiratory failure or ARDS. Based on the results of this study, the authors are interested in researching to see the relationship between CRP and LDH on the degree of severity, and their use as a predictor of death in confirmed COVID-19 patients.

Material and Methods

In this analytical inquiry, a cross-sectional design was employed to determine whether or not CRP and LDH were able to accurately predict mortality in COVID-19 patients hospitalized at Arifin Achmad Hospital Pekanbaru illness severity and outcome. This study was carried out in September 2021 utilizing the data obtained from medical records during April 2020 and July 2021. Patients who meet the inclusion criteria were included in this study. The medical records of 18-year-old adult Covid-19 patients who were hospitalized at the Pinere room of Arifin Achmad General Hospital, with moderate, severe, or critical illness served as the inclusion criteria for this study.

The gathered data were examined by utilizing the statistical package designed specifically for the social sciences (SPSS), version 26. Categorical data were analyzed using univariate methods, the results were expressed in terms of number and frequency. When numerical data were normally distributed, it will be reported as mean and standard deviation. Otherwise, the median (maximum and minimum values) was used when the data were not normally distributed. The bivariate analysis in this study used the chi-square test. On the receiver operating characteristic (ROC) curve, we did an area under curve analysis using the area under curve (AUC) notation.

Results and Discussion

There were 1,109 samples total that was examined for CRP and LDH at the Arifin Achmad Hospital during the data collection period that lasted from April 2020 to July 2021. The data that was used as a sample for this study were separated into severe and non-severe categories. The data of patients who did not satisfy the criteria were excluded from the sample until a total of 522 samples were collected. This research included 403 samples of participants aged 18 to 59 (representing 77.2% of the total), as well as 36 samples of participants aged 60 and older (representing 22.8% of the total). There are 267 male samples, which constitute 51.1% of the total, and 255 female samples, which constitute 48.9%. A total of 383 samples were categorized as non-severe (73.4%), while 139 samples were classified as severe (26.6%). A summary of the patient's features, is listed in Table 1.

Table 1. Characteristics of patients

Variable	n	%	Mean	STDV
Age (years)				
18 – 59	403	77,2		
≥ 60	119	22,8		
Gender				
Man	267	51,1		
Woman	255	48,9		
Severity of Disease				
Severe	139	26,6		
Non-Severe	383	73,4		
CRP, u/L			20.40	(0.1-449.8)
High	399	76.4		
Normal	123	23.6		
LDH, u/L			239.50	192.64
High	301	57.7		
Normal	221	42.3		
Outcome				
Survive	449	86.0		
Not survive	73	14.0		

It was discovered that males made up the majority of responses, accounting for 51.1% of the total. The findings of this study are comparable to those obtained by Zhou et al. (2020), Qin et al. (2020), and colleagues in Wuhan from a sample of 191 COVID-19 patients; of those patients, 62% were male and 38% were female. These findings are comparable to those obtained by Tan et al. (2020) in Changsa, albeit with some minor distinctions. The majority of COVID-19 patients were female (59%), while male patients made up 41% of the total. According to data compiled by the Ministry of Health in September 2021, the largest percentage of COVID-19 patients was found to be 50.9% female and 49.1%, male. Because gender is not a risk factor for COVID-19 infection, the sex distribution does not have a substantial difference that is significant in this study (Tjahyadi et al., 2020).

According to the study of COVID in the United States, China, and Europe, the clinical manifestations of COVID-19 range from asymptomatic or mild upper respiratory tract disease to moderate and severe disease, rapidly progressive pneumonitis, respiratory failure, and respiratory distress. Asymptomatic or mild upper respiratory tract disease is the least severe form of COVID-19 infection. Acute syndrome, as well as the failure of many organs, leads to catastrophic consequences. The natural history of the disease can be broken down into four distinct phases, beginning with incubation and progressing to critical illness. During each phase, factors such as coagulopathy, an exacerbated immune response, and the direct cytotoxic effects of SARS-CoV-2 all play an important part in the progression of severe disease (Melenotte et al., 2020).

Only 73 patients, or 14% of the total, passed away while they were receiving treatment; the other patients were discharged successfully. The mean LDH and CRP levels of the patients in this study were 293.47 ± 192.64 u/L and 55.48 ± 79.03 u/L, respectively. According to the findings of this study, the mean levels of CRP in patients who passed away were significantly greater than the mean levels of CRP in patients who exhibited signs of improvement (312.27 vs. 253.24 u/L, p < 0.001). LDH levels of patients who died were higher than patients who had improved (326.84 vs 288.04 u/L, p <0.001). The area under the curve (AUC) ROC (figure 2) for patient outcomes on LDH and CRP examinations was 0.74 and 0.80 with cut-off levels of LDH and CRP to predict mortality in COVID-19 patients of 297 u/L (sensitivity, specificity, PPV, NPV = 60.2%, 53.9%, 17.5%, and 89.3%) and 52 u/L (sensitivity, specificity, PPV, NPV= 63.0%, 78.1%, respectively, 31.9%, and 92.8%) with p-values for all results <0.001. This value is different when we use the cut-off used by Arifin Achmad hospital, where the sensitivity, specificity, PPV, and NPV of CRP (17,5%, 97,5%, 95,8%, and 26,7%), respectively. The sensitivity, specificity, PPV, and NPV of LDH to the incidence of death when using the Arifin Achmad hospital cut-off were (20,6 %, 95,0%, 84,9%, and 46,7%), respectively.

This study found that factors such as age and gender do not correlate with the concentration of CRP; the increase in CRP levels has a positive correlation with the degree of inflammation. An elevated CRP level may also boost complement activity and phagocytosis, both of which might assist the body in eliminating dangerous bacteria that have attacked it. The levels of CRP in the blood can be used to make an initial diagnosis of pneumonia, and people with severe pneumonia have higher levels of CRP in their blood. This evaluation is an important indicator that should be looked for during the diagnostic process and evaluation of severe lung sickness (Tjahyadi et al., 2020; Sadeghi-Haddad-Zavareh et al., 2021).

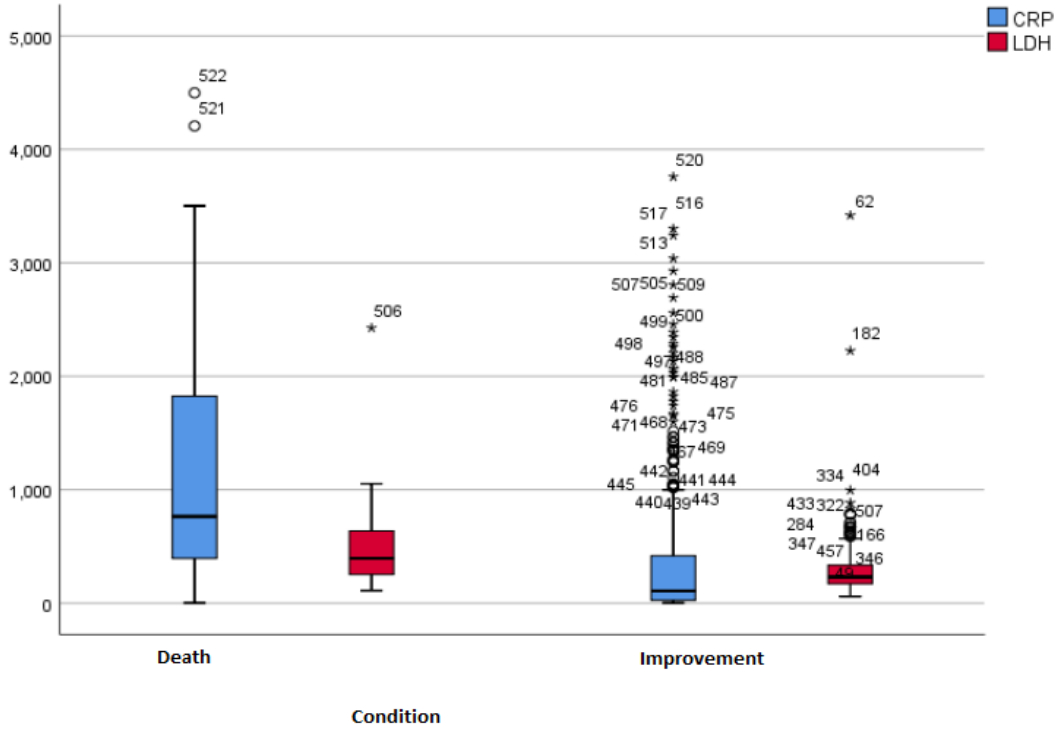

Figure 1. Comparison between CRP and LDH levels in patients who died and recovered

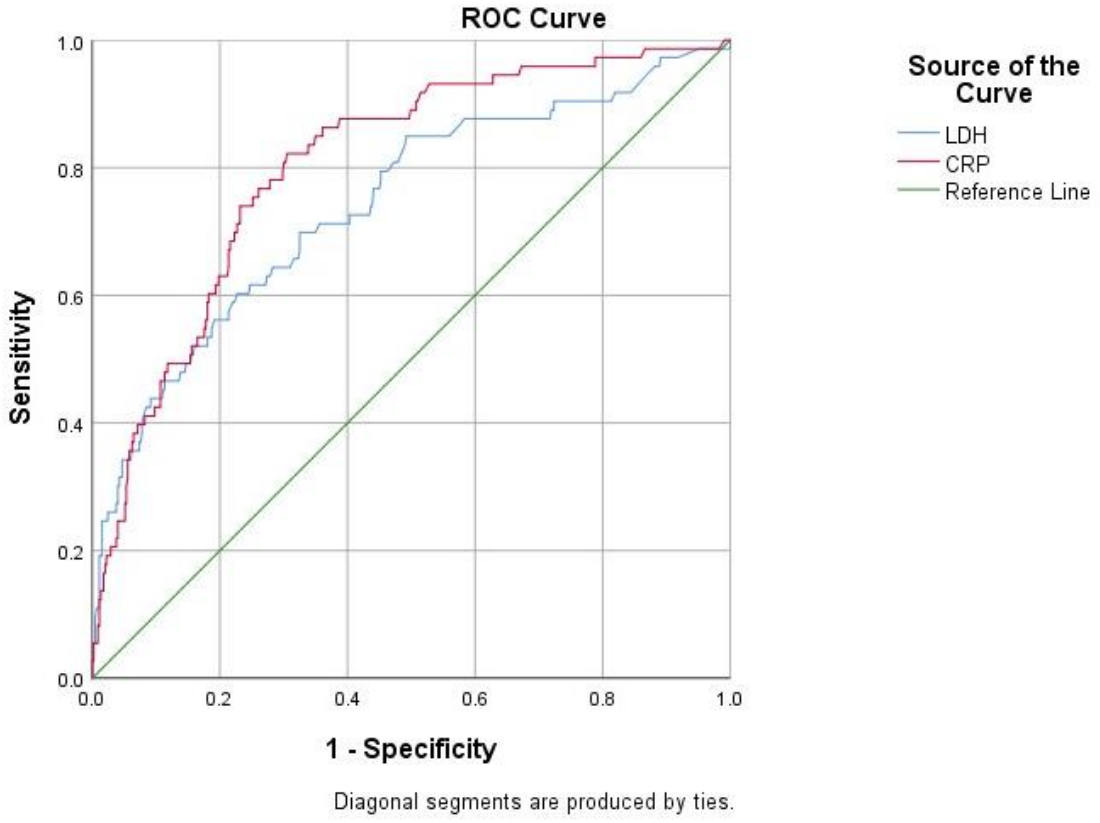

Figure 2. AUC of ROC curve analysis

A poor prognosis is associated with elevated serum levels of the enzyme LDH in several different diseases, the most notable of which are tissue inflammation and damage to the lung parenchyma. After the tissue has been damaged, levels of LDH are created, and these levels have been linked to a range of pathophysiological processes. In many different diseases, LDH functions as a biomarker of cellular death that is not disease-specific. At the time of diagnosis, a static assessment was performed on several prognostic variables, one of which was LDH (Wang et al., 2021; Tjahyadi et al., 2020; Li et al., 2020).

Conclusion

Testing for CRP and LDH can both be used to predict death, but according to this study, testing for CRP is more accurate than testing for LDH.

Acknowledgment

These should be included at the end of the text and not in the footnotes. Personal acknowledgments should precede those of institutions or agencies.

References

Ali, A. H. M., Mohamed, S. O. O., Elkhidir, I. H. E., Elbathani, M. E. H., Ibrahim, A. A. H., Elhassan, A. B. E. et al. (2020). The association of lymphocyte count, crp, d-dimer, and ldh with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Sudan J Med Sci.,15*(2), 9–23. DOI:10.18502/sjms.v15i5.7146

Centers for Disease Control and Prevention. (2020). *2019 Novel coronavirus (2019-nCoV).* Washington DC.

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol., 39*(5), 529–39. doi: 10.1007/s00281-017-0629-x.

Chua, R. L., Lukassen, S., Trump, S., Hennig, B. P., Wendisch, D., Pott, F., et al. (2020). COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol., 38*(8), 970–9. doi: 10.1038/s41587-020-0602-4

Del Valle, D. M., Kim-Schulze, S., Huang, H-H., Beckmann, N. D., Nirenberg, S., Wang, B. et al. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med., 26*(10), 1636–43. doi.org/10.1038/s41591-020-1051-9

Di Gennaro, F., Pizzol, D., Marotta, C., Antunes, M., Racalbuto, V., Veronese, N. et al. (2020). Coronavirus diseases (Covid-19) current status and future perspectives: A narrative review. *International Journal of Environmental Research and Public Health, 17* (8), 2690. doi: 10.3390/ijerph17082690.

Fang Z, Yi, F., Wu, K., Lai, K., Sun, X., Zhong, N. et al. (2020). Clinical characteristics of coronavirus disease 2019 (Covid-19): An updated systematic review. *medRxiv,* doi.org/10.1101/2020.03.07.20032573

Gaebler, C., Wang, Z., Lorenzi, J. C. C., Muecksch, F., Finkin, S., Tokuyama, M. et al. (2021). Evolution of antibody immunity to SARS-CoV-2. *Nature, 591*(7851), 639–44. doi: 10.1038/s41586-021-03207-w

Gorbalenya, A. E. (2020). Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. *BioRxiv., 2*(7), 93–7.

Henry, B., Aggarwal, G., Wong, J., Benoit, S., Vikse, J., & Plebani, M. (2 0 2 0) . Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am J Emerg Med*., *38*(9), 1722-6. doi: 10.1016/j.ajem.2020.05.073.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y. et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 395*(10223), 497–506. doi: 10.1016/S0140-6736(20)30183-5

Li, C., Ye, J., Chen, Q. et al. (2020). Elevated Lactate Dehydrogenase (LDH) level as an independent risk factor for the severity and mortality of COVID-19. *Aging, 12*(15), 15670–81. doi: 10.18632/aging.103770

Lingeswaran, M., Goyal, T., Ghosh, R., Suri, S., Mitra, P., Misra, S., et al. (2020). Inflammation, Immunity and immunogenetics in COVID-19: A narrative review. *Indian Journal of Clinical Biochemistry, 35,* 260–73.

Melenotte, C., Silvin, A., Goubet, A. G. et al. (2020). Immune responses during COVID-19 infection. *Oncoimmunology, 9*(1), 1–23. doi: 10.1080/2162402X.2020.1807836.

Mueller, A., Tamura, T., Conor, P., Crowley, P., Anthony, F., Massaro, et al. (2020). Inflamatory biomarker trends predict respiratory decline in COVID-19 patients. *Cell Reports Medicine*, 144, 1-8. doi: 10.1016/j.xcrm.2020.100144.

Pogiali, E., Domenica, Z., Paolo, I., Luca, R., Giulia, L., Dacrema, A. et al. (2020). Lactate dehydrogenase and C-Reactive Protein as predictors of respiratory failure in CoVID- 19 patients. *Clinica Chimica Acta J*., *10,* 1-10. doi: 10.1016/j.cca.2020.06.012

Pons, M. J., Ymaña, B., Mayanga-Herrera, A., Sáenz, Y., Alvarez-Erviti, L., Tapia-Rojas, S, et al. (2021). Cytokine profiles associated with worse prognosis in a hospitalized peruvian COVID-19 cohort. *Frontiers in Immunology, 12*. doi.org/10.3389/fimmu.2021.700921

Qin, C., Zhou, L., Hu, Z. et al. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in wuhan, China. *Clin Infect Dis., 71*(15), 762–8. doi: 10.1093/cid/ciaa248.

Sadeghi-Haddad-Zavareh, M., Bayani, M., Shokri, M., et al. (2021). C-Reactive Protein as a Prognostic Indicator in COVID-19 Patients. *Interdiscip Perspect Infect Dis*., *7*(8), 61–9. doi: 10.1155/2021/5557582

Salehi, S., Abedi, A., Balakrishnan, S., Gholamrezanezhad, A. (2020). Coronavirus disease 2019 (Covid-19): A systematic review of imaging findings in 919 Patients. *Am J Roentgenol., 215*(1), 87–93. doi: 10.2214/AJR.20.23034.

Tan, C., Huang, Y., Shi, F., Tan, K., Ma, Q., Chen, Y, Jiang X et al. C-Reactive protein correlates with computed tomographic finding and predicts severe COVID-19 early. *J Med Virol*, *92*, 856-62. doi: 10.1002/jmv.25871.

Tan, L., Wang, Q., Zhang, D. et al. (2020). Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. *Nat Res J., 5*(33), 1–3. doi: 10.1038/s41392-020-0148-4.

Tjahyadi, R. M., Astuti, T., & Listoko, A. S. (2020). COVID-19 :Correlation between CRP and LDH to disease severity and mortality in hospitalized COVID-19 patients. *Medica Hosp., 7*(1), 71–9. doi.org/10.36408/mhjcm.v7i1A.467

Tjahyadi, R., Astuti, T., & Sri, A. (2 0 2 0) . COVID 19: Correlation Between CRP and LDH to Disease Severity and Mortality in Hospitalized COVID-19 Patients. *Med Hosp*., *7*, 144-9. Doi.org/10.36408/mhjcm.v7i1A.467

Wang, L., Yang, L. M., Pei, S. F., Chong, Y. Z., Guo, Y., Gao, X. L. et al. (2021). CRP, SAA, LDH, and DD predict poor prognosis of coronavirus disease (COVID-19): a meta-analysis from 7739 patients. *Scand J Clin Lab Invest., 81*(8), 679–86. doi: 10.1080/00365513.2021.2000635

World Health Organization (WHO). (2020). *Novel Coronavirus (2019-nCoV): Situation report*. Geneva.

Zhou, F., Yu, T., Du, R. et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet, 395*(10229), 1054–62. DOI:10.1101/2020.02.07.937862