Correlation between Lactate Dehydrogenase and Severity Clinical Degree of COVID-19 Patients

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Abstract: ***Background**: Elevated serum lactate dehydrogenase (LDH)occurs in clinical conditions such as severe infection in COVID-19.[1]LDH is present in the lung tissue so that the occurrence of severe pneumonia causes the release of larger amounts of LDH which indicates the severity of COVID-19.[2] This study aims to analyzed correlation between lactate dehydrogenase and severity clinical degree of COVID-19 patients who hospitalized at Adam Malik General Hospital, Medan, Indonesia. **Materials and Methods**: This study is an observational analytical study with a cross-sectional study design. We analyzed laboratory tests to identify tissue damage and inflammatory status in 180COVID-19 patients (50.6% males and 49.4% females) admitted to Department of Pulmonology and Respiratory Medicine, Adam Malik General Hospital. We investigated the relationship between LDH values(normal range < 353.5 U/L)[3] and severity clinical degree (moderate, severe and critical) of COVID-19 patients. Statistical analysis was used chi-square test. **Results**: Patients had mean age moderate COVID-19 of 44 years, severe 55 years and critical 55 years. LDH levels were significantly correlated with gender (p=0.003); age (p = 0.032);and disease phase (p=0.000) of COVID-19 patients.LDH levels were not significantly correlated with comorbid COVID-19 patients (p=0,310).LDH levels were significantly correlated with the disease degree of COVID-19 patients (p = 0.000). **Conclusion**: There is correlation between lactate dehydrogenase and severity clinical degree of COVID-19 patients who hospitalized at Adam Malik General Hospital, Medan, Indonesia.***

Keywords: COVID-19, LDH, disease degree

1. Introduction

The coronavirus pandemic of 2019 (COVID-19) is caused by the acute respiratory syndrome coronavirus 2 (SARS CoV-2) and is rapidly spreading around the world. Early symptoms of COVID-19 mainly include fever, cough, myalgia, fatigue, or dyspnea. In the advanced stages of the disease, dyspnea may develop and gradually progress to acute respiratory distress syndrome (ARDS) or multi-organ failure. It has been reported that cytokine storms are associated with many diseases, such as SARS and MERS. The cytokine storm caused by COVID-19 is thought to be related to the severity of COVID-19.[1, 2]

Various biomarkers are currently being investigated for their role in determining prognosis in patients with COVID-19.3 Lactate dehydrogenase (LDH) is one of the biomarkers that can be assessed in patients with infections, especially viral infections. LDH is an enzyme involved in the conversion of lactate to pyruvate in the cells of most body tissues and increases after tissue damage. Elevated serum LDH appears in various clinical conditions, such as hemolysis, cancer, severe infections and sepsis, liver disease, hematological malignancies, and other diseases.[3] The enzyme lactate dehydrogenase is widely distributed in the body and is required to identify clinical situations in which lactate determination dehydrogenase and its isoenzymes in serum have significant values. LDH isoenzyme profile is an isoenzyme profile that is commonly used to detect certain organ damage. From a clinical perspective, the determination of serum isoenzyme activity is very important, but its determination in biological materials from various tissues and organs is also very important.[65]

The production of cytokines and LDH can cause tissue damage, which can lead to serious infections. Patients with severe COVID-19 infection may produce more LDH in the blood because LDH is present in the lung tissue (isozyme 3), as the disease is characterized by a severe type of interstitial pneumonia that generally leads to acute respiratory distress syndrome. However, the contribution of different LDH isoenzymes to the observed increase in LDH in COVID-19 has not been established. Thrombotic microangiopathy, which is associated with kidney failure and cardiac injury and may be caused by COVID-19 infection, also has elevated LDH levels.[11,68]

The use of biomarkers in medicine lies in their ability to detect disease and support diagnostic and therapeutic decisions. Clinically useful biomarkers can complement clinical diagnosis and assist in disease monitoring, treatment evaluation, and prediction of prognosis and health outcomes. Changes in plasma or serum enzymes and isoenzymes are useful indicators of tissue damage in many diseases. Elevated enzymes are usually associated with their leakage from damaged cells.[7]

The results of the analysis of several studies show an association between increased LDH values and poorer outcomes in patients with COVID-19.[10] Patients with severe COVID-19 infection are predicted to release greater amounts of LDH into the circulation due to the location of LDH in the lungs.[11]

2. Methods

2.1 Research Methodology

This study is an observational analytical study with a cross-sectional study design to assess the relationship between LDH levels and the severity of COVID-19 patients at Haji Adam Malik General Hospital Medan. Data collection was carried out through the medical records of patients who had confirmed COVID-19 from the results of the RT-PCR examination and examination of the patient's LDH serum levels.

Population and Samples

The target population in this study were all confirmed COVID-19 patients through RT-PCR examination. The sampling technique was non-probability sampling, namely the consecutive sampling technique, with a total sample size of 80 subjects.

Data Analysis

The data that has been collected will be analyzed using a statistical data processing application. The stages of data analysis included univariate analysis, which was carried out to determine the frequency of each dependent and independent variable. For variables with categorical data types, they are presented in frequency values (percentages). The analysis was continued with bivariate analysis to assess the relationship between LDH levels and the severity of COVID-19 using the Chi Square test and conducting a non-parametric test with the Kruskal Wallis test to test whether there was a significant difference between the independent variable group and the dependent variable.

3. Result

In this study, 180 medical records of patients with a diagnosis of COVID-19 were taken from April 2021 to December 2021. Tables 1 and 2 show the demographic characteristics of the patients. Based on age, the age group 46–59 years old is the age group with the most COVID-19 patients with 65 people (36.1%). Age 18-30 years, up to 23 people (12.8%), 31-45 years, up to 31 people (17.2%), and > 60 years, up to 61 people (33.9%). Based on gender, men were the most, which was 91 people (50.6%), and females were 89 people (49.4%). In men, most of the patients had severe and critical degrees of each, as many as 34 people, and in women, the majority of patients had moderate degrees of COVID-19, as many as 37 people.

Table 3 shows the distribution of comorbidities that COVID-19 patients have. Based on the comorbidities of the study subjects and the severity of COVID-19, 102 people (56.67%) of COVID-19 patients had no comorbidities. In patients without comorbidities, most of them had a moderate degree of COVID-19. Patients with COVID-19 who had comorbidities were found to have comorbid hypertension (31 people) and DM (22 people). In hypertension comorbid patients, 31 people (17.2%) and 14 people (7.8%) experienced a critical degree. Meanwhile, in DM comorbid patients, there were 22 people (12.2%), with 9 (5%) experiencing severe COVID-19 symptoms. There were several other comorbidities found in this study, such as patients with COVID-19 who had comorbid hyperthyroidism, consisting of 1 person (0.5%) to a mild degree. COVID-19 patients who have comorbid hypertension and CHF consist of 1 person (0.5%) at a critical level. Patients with COVID-19 who have comorbid HIV consist of 1 person (0.5%) to a mild degree.

In Table 4, which shows the distribution of LDH levels in patients with COVID-19, 72 people (40.0%) had abnormal LDH levels, where in Table 5 it was explained that abnormal LDH levels were found to be 14.4% in men and as many as 25.9 % in women. The results of the chi-square test obtained a p value of 0.003 (0.05), meaning that there is a significant relationship between LDH levels and the sex of COVID-19 patients. Meanwhile, based on the age group (table 6), the most abnormal LDH levels occurred in the 46-59 year age group (14.4%) followed by the 60-year age group (9.4%). In the 18-30 year age group, there were 7.8% of patients who had abnormal LDH levels, and at the age of 31-45 years, there were 8.3%. The results of the chi-square test obtained a p value of 0.032 (0.05), meaning that there is a significant relationship between LDH levels and the age of COVID-19 patients.

In Table 8, we can see that the highest average LDH level is found in patients with a critical illness degree of 614.33. The lowest average LDH level was found in patients with moderate disease degrees of 302.06. The average LDH level in patients with severe disease was 472.80, which was higher than patients with moderate and lower than patients with critical illness. The higher the degree of disease, the higher the LDH level. Then it can be seen in table 9, the most abnormal LDH levels occurred in moderate-grade patients (27.8%), followed by severe patients (8.9%), and critical patients (3.3%). The results of the chi-square test obtained a p value of 0.000 (0.05), meaning that there is a significant relationship between LDH levels and the degree of illness of COVID-19 patients.

4. Discussion

According to the findings of this study, male COVID-19 patients outnumber females (51.1%). These results are in line with the research conducted by Karyono and Wicaksana in Indonesia that found COVID-19 patients were more prevalent in males (54.6%) than females (45.4%). 75. According to Ahmed and Dumanski, these results could be caused by the enzyme angiotensin 2 (ACE2), which is an integral part of the human renin-angiotensin-aldosterone system (RAAS). The RAAS is a functional receptor that allows SARSCoV-2 to invade human alveolar epithelial cells. Overall, males exhibited greater RAAS activity than females.

According to Liu et al., the average age of patients with severe and critical degrees is higher than moderate degrees.[74] This is in line with this study where the average age of patients with moderate degrees is 45 years, while the age of COVID-19 patients with severe and critical degrees is 55 years.[56] According to Wu et al., this may be due to a decrease in the body's resistance in old age so that it has a greater risk of ARDS and death.[78]

Patients in this study had several comorbidities, including the most common comorbidities of diabetes mellitus and hypertension. The results of Akhtar et al.'s study showed that diabetes and other comorbidities were significant predictors of morbidity and mortality in COVID-19 patients.[79] According to Wang et al., SARS-CoV-2 infection in patients with diabetes triggers a higher stress condition, with the release of hyperglycemic hormones. glucocorticoids and catecholamines, which cause elevated blood glucose and abnormal glucose variability.[80]Conditions of hyperglycemia and insulin resistance increase the synthesis of glycosylated end products (AGEs) and pro-inflammatory cytokines and oxidative stress, in addition to stimulating the production of adhesion molecules that promote mediate tissue inflammation. This inflammatory process aggravates diabetes patients. Uncontrolled diabetes indicates that lung epithelial cells will be exposed to high glucose, significantly increasing infection and replication.[79]

The mortality rate for COVID-19 patients with hypertension co-morbidities tends to be higher. This is also supported by Huang et al., who found that hypertension is significantly associated with independent risk for predicting the severity and mortality of COVID-19 patients.[80]This could be due to direct injury mediated through angiotensin converting enzyme 2 (ACE2). A study in China showed that SARS-CoV-2 infection was caused by the binding of viral proteins to the ACE2 receptor after protein activation. ACE2 is a monocarboxypeptidase best known for cleaving several peptides in the renin-angiotensin system. Since its discovery in 2000, ACE2 has been considered a protective factor against elevated blood pressure. Binding of SARS-CoV-2 to ACE2 can reduce the physiological function of ACE2, and then lead to adverse outcomes of hypertension such as multi-organ dysfunction.[81] In addition, ACE2 plays an important role in acute lung disease, especially acute respiratory distress syndrome.[82]

In this study, LDH levels were examined in COVID-19 patients. Lactate dehydrogenase is an enzyme that is present in almost all bodily tissues. LDH (EC 1.1.1.27) is a hydrogen-transferring cytoplasmic enzyme that catalyzes the oxidation of L-lactate to pyruvate with nicotinamide-adenine dinucleotide (NAD)+ as a hydrogen acceptor, which is the final reaction of the anaerobic glycolysis pathway. The main types of LDH expressed in a given tissue depend on their metabolic needs; LDH-1 and LDH-2 are predominantly expressed in the heart, kidney, and erythrocytes; LDH-4 and LDH-5 in the liver and skeletal muscle; and the intermediate-mobility isoenzyme LDH in the spleen, lymph nodes, leukocytes, and platelets. LDH-3 is prevalent in lung tissue. Severe infections can cause tissue damage caused by the production of cytokines with subsequent release of LDH into the bloodstream. In this context, it has been proposed that the major LDH isoform in lung tissue, LDH-3, is released in greater amounts in more severely affected COVID-19 patients due to a severe form of interstitial pneumonia (often progressing to acute respiratory distress syndrome). That is the hallmark of this disease. [92]

In this study, the LDL level of COVID-19 patients was 459.35, which is greater than 255, which indicates an abnormal condition. Research conducted by Yan et al. showed that there is an increase in lactate dehydrogenase (LDH) in the blood, strongly indicative of COVID-19 death. At 8, LDH levels are elevated due to multiple organ injury and failure with decreased oxygenation.[94]

In this study, it was found that there was a significant relationship between LDH levels and gender. The average LDH level of men is greater than that of women, but abnormal LDH levels are more common in women. Research by Hu et al. demonstrated that serum LDH and male sex were independent prognostic factors for patients with COVID-19.[95] This could be related to sex hormone conditions as factors that impair immune and inflammatory responses or thrombotic diathesis and, consequently, as negative prognostic factors for severity. and the results of COVID-19.[96] In this study, abnormal LDH levels were more common in women than in men. This could be due to the influence of age and comorbidities that were not controlled in this study so that they could affect LDH levels.

In this study, it was found that there was a significant relationship between LDH levels and age. LDH levels are getting higher with increasing age, and abnormal LDH levels are most common in the 46-59 year age group. The results are in line with the research of Hu et al. in China that found a significant difference in LDH levels between COVID-19 patients aged less than 60 years and patients aged more than or equal to 60 years.[100] Patients with normal aging experience decreased physiological immune function, and immunosuppression phenomena tend to occur in patients who are older. elderly patients, making it difficult for patients to control the pro-inflammatory response.[102] The presence of comorbidities in elderly patients can also be a cause of multiple organ injuries that can increase LDH levels.[94]

The results of this study indicate that there is no significant difference in the average LDH levels in COVID-19 patients based on comorbidities. These results are in line with the research of Martha et al. that showed an increase in LDH and a poor prognosis for COVID-19 are not influenced by comorbid hypertension or diabetes.[103] This is because an increase in LDH is associated with comorbidities. LDH is associated with diabetes because of decreased glycogen synthesis, altered oxidative metabolism of glucose, and an increased rate of whole-body non-oxidative glycolysis. This mechanism causes an increase in lactate in patients with insulin resistance compared to those without. [104]

In this study, LDH levels were significantly related to the degree of COVID-19 disease, where the greater LDH levels indicated the higher severity of COVID-19, but abnormal LDH levels were most common in moderate disease degrees. These results are in line with the research of Hu et al. that showed that COVID-19 patients with severe cases had higher serum LDH levels than non-severe COVID-19 patients.[100]Elevated LDH levels are an independent risk factor for COVID-19 severity and mortality.[110] LDH has been shown to be a potential prognostic biomarker in patients with COVID-19. Elevated LDH indicates tissue hypoperfusion, indicating the extent of disease, which can affect prognosis.[111] The level of LDH reflects the degree of cell damage and tends to increase with the increasing severity of infection. [109] An increase in LDH in patients with COVID-19 indicates lung and tissue injury. It can cause disruption of tissue perfusion, which can lead to multiple organ failure due to various mechanisms, including thrombosis, and trigger an increase in LDH. [108]

5. Conclusion

In this study, there was a significant relationship between LDH levels and the severity of COVID-19 (P 0.05). It was also found that patients with COVID-19 were more likely to be males and most of them had severe and critical symptoms. The average age of most patients COVID-19 sufferers in the range of 46 to 59 years.

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Tables

Table 1: Frequency distribution of research subjectsage

Age (Years)	Total	Percentage
18-30	23	12,8
31-45	31	17,2
46-59	65	36,1
≥ 60	61	33,9
Total	180	100

Table 2: Frequency distribution of research subjects' gender based on the severity of COVID-19 disease

Sex	Degree			Total (%)
	Moderate	Severe	Critical	
Man	23	34	34	91 (50,6)
Woman	37	26	26	89 (49,4)
Total	60	60	60	180 (100)

Table 3: Frequency distribution of research subjects' Comorbidity based on the severity of COVID-19 disease

Comorbidity	Degree			Total (%)
	Moderate	Severe	Critical	
Nothing	40	31	31	102 (56,67)
DM,HT	3	9	7	19 (10,55)
DM	7	9	6	22 (12,22)
DM,CKD	0	1	0	1 (0,55)
HT	8	9	14	31 (17,22)
CKD	0	1	1	2 (1,10)
Hipertiroid	1	0	0	1 (0,55)
HT,CHF	0	0	1	1 (0,55)
HIV	1	0	0	1 (0,55)
Total	60	60	60	180 (100,00)

Table 4: Frequency distribution of LDH Levels

LDH Level	Total	Percentage
Normal	108	60,0
Tidak normal	72	40,0
Jumlah	180	100

Table 5: The Relationship of Sex with LDH Levels of Research Subjects

Sex	abnormal		Normal		Total		p-value
	f	%	f	%	f	%	
Man	26	14,4	65	36,1	91	50,6	0,003
Woman	46	25,6	43	23,9	89	49,4	
Total	72	40,0	108	60,0%	180	100	

Table 6: The Relationship of Age with LDH Levels of Research Subjects

Age (Year)	Abnormal		Normal		Total		p-value
	f	%	f	%	f	%	
18-30	14	7,8	9	5,0	23	12,8	0,032
31-45	15	8,3	16	8,9	31	17,2	
46-59	26	14,4	39	21,7	65	36,1	
≥ 60	17	9,4	44	24,4	61	33,9	
Total	72	40,0	108	60,0	180	100	

Table 7: The Relationship of Comorbids with LDH Levels of Research Subjects

Comorbidity	Abnormal		Normal		Total		p-value
	f	%	F	%	f	%	
Have comorbidity	27	15,0	50	27,8	77	57,2	0,310
Have no comorbidity	45	25,0	58	32,2	103	42,8	
Total	72	40,0	108	60,0	180	100	

Table 8: Average LDH Levels by COVID-19 Severity

Degree	N	LDH Levels		Mean±SD
		Min	Maks	
Moderate	60	113,04	2971,00	302,06 ± 367,34
Severe	60	151,00	1128,00	472,80 ± 201,12
Critical	60	208,00	1133,00	614,33 ± 207,11

Table 9: Relationship COVID-19 Severity with Levels of LDH

Degree	Abnormal		Normal		Total		p-value
	f	%	f	%	f	%	
Moderate	50	27,8	10	5,6	60	33,3	
Severe	16	8,9	44	24,4	60	33,3	0,000
Critical	6	3,3	54	30,0	60	33,4	
Total	72	40,0	108	60,0	180	100	

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