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Lactate Dehydrogenase Levels as A Marker of COVID-19 Severity

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Knowing the severity of COVID-19 is important during a pandemic. Measurement of Lactate Dehydrogenase (LDH) levels is a simple, quick, and widely available laboratory test in most health facilities. Lactate dehydrogenase levels change significantly in patients with tissue damage including COVID-19 disease. The purpose of this study was to analyze the LDH levels as a marker of the severity of COVID-19. The research method used was a cross-sectional approach using primary data from 70 suspected COVID-19 patients from June to July 2021 at Labuang Baji Hospital, Hasanuddin University Hospital, and Makassar City Hospital. Samples were grouped into mild, moderate, and severe COVID-19. The LDH levels at the time of hospital admission were measured using an Architect device. Chi-Square, Kruskal-Wallis, and ROC curve statistical tests were used to obtain the LDH value with a significant value of $p<0.05$. The sample consisted of 24 mild COVID-19, 23 moderate COVID-19, and 23 severe COVID-19. The LDH levels in mild COVID-19 were 101.00 U/L (74.00-156.00 U/L) significantly different from moderate COVID-19 was 143.00 U/L (126.00-253.00 U/L) and COVID-19 were 291.00 U/L (177.00-655.00 U/L) ($p<0.001$) and had a very strong positive correlation ($r=0.914$). The ROC curve showed that LDH had a sensitivity of 91.3%, specificity of 94.7% with the cut-off >250.5 U/L, NPV of 96.4%, PPV of 87.5%, and accuracy of 91.3%. LDH levels increase along with the increasing severity of COVID-19 caused by tissue damage due to increased inflammatory response. LDH can be used as a marker of COVID-19 severity.

Keywords: COVID-19, lactate dehydrogenase, marker

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 virus is a new type of Coronavirus that has never been previously identified in humans. The spread of SARS-CoV-2 from human to human is known as the main mode of transmission leading to a more aggressive spread. Transmission of SARS-CoV-2 from symptomatic patients occurs through droplets released when coughing or sneezing. Common signs and symptoms of COVID-19 infection include symptoms of acute respiratory distress such as fever, cough, and shortness of breath. The average incubation period is 5-6 days and the longest incubation period is 14 days. Severe cases of COVID-19 can cause acute respiratory distress/failure syndrome and even death.[1-4]

The diagnosis of COVID-19 is established from the anamnesis of any history of travel to endemic areas or any history of close contact with COVID-19 patients, any clinical symptoms leading to pneumonia, to radiological and laboratory tests. The gold standard in diagnosing Covid-19 is the molecular identification of SARS-CoV-2 by nucleic acid amplification methods by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or by viral genome sequencing. However, with limited facilities and human resources, broad molecular identification cannot be carried out in all laboratories, causing delayed diagnosis and treatment of COVID-19. Measurement of Lactate Dehydrogenase (LDH) levels is a simple, quick, and widely available laboratory test in most health facilities. Lactate dehydrogenase levels change significantly in patients with tissue damage including COVID-19 disease.[1,5-9]

There have been many studies, which reported an increased LDH in severe cases of death, especially in cases involving cardiac injury. As research on COVID-19 increases worldwide, many studies have found that LDH is associated with the severity of COVID-19. A study by Shi *et al.* found that high LDH levels were an independent risk factor for exacerbations in mild COVID-19 patients. In another study performed in the Jiangsu Province of China,

Huang *et al.* found that patients with severe conditions had higher LDH levels than patients with mild conditions. Research by Li *et al*. on 26 patients with severe conditions and 43 patients with mild conditions found similar results; there was an increase in LDH levels in patients with severe conditions compared to mild conditions.[5,6,10]

Although research on LDH levels in COVID-19 patients has been reported in several journals, reports on the relationship between LDH levels and the severity of COVID-19 disease in Indonesia remain limited.

METHODS

This research was a cross-sectional study by taking primary data from 102 patients at Labuang Baji Hospital, Hasanuddin University Hospital, and Makassar City Hospital. The study population of patients was all patients admitted with suspected COVID-19 at Labuang Baji Hospital, Hasanuddin University Hospital, and Makassar City Hospital from June to July 2021. The research sample of 70 subjects was an accessible population, which had the results of the Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test at Labuang Baji Hospital, Hasanuddin University Hospital, and Makassar City Hospital, aged 18-79 years, and met the exclusion criteria such as subject had no history of myocardial infarction, skeletal muscle disorders, hemolytic anemia, and malignancy.

Patients were further classified into COVID-19 criteria based on severity (clinical symptom criteria) as follows: Mild illness: patients with non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, and muscle aches; Moderate illness: patients with clinical symptoms of fever, cough, and dyspnea (frequency 20-30 times/minute) and no signs of severe pneumonia; Severe illness: patients with fever or were under surveillance for respiratory infections, supported with one of: tachypnea (respiratory rate >30 breaths/min), severe respiratory distress or patient oxygen saturation < 90%. Lactate dehydrogenase levels were measured in the serum of patients with COVID-19 using the Architect analyzer with a reference value of < 250 U/L.

Data analysis was performed using the SPSS version 22. Statistical analysis methods used were descriptive statistical calculations, the Chi-Square test, and the Kruskal-Wallis test. The test results with $p < 0.05$ were significant. The data were also analyzed using the Receiver Operating Characteristics (ROC) curve to assess LDH as a marker of the severity of COVID-19.

Approval of ethical feasibility was obtained from the Health Research Ethics Commission, Faculty of Medicine, Hasanuddin University/Hasanuddin University Hospital/Dr. Central General Hospital Wahidin Sudirohusodo, Makassar with number 394/UN4.6.4.5.31/PP36/2021.

RESULTS AND DISCUSSIONS

A total of 70 patients with confirmed COVID-19 were involved as research subjects with ages ranging from 21-65 years with a maximum age of 41-60 years. Based on gender, most of the research subjects in this study were 39 females (55.7%). A total of 51 patients (72.9%) had no comorbidities and 9 patients (27.1%) had comorbidities with the most common comorbidities reported in this study were Diabetes Mellitus (DM) found in 9 patients (12.7%), Non-Hemorrhagic Stroke (NHS) found in 3 patients (4.3%), Hypertension (HT) found in 3 patients (4.3%), Chronic Kidney Disease (CKD) found in 2 patients (2.9%), and Pulmonary Tuberculosis (TB) found in 2 patients (2.9%). Based on the degree of disease, most of the research subjects had a mild illnesses with a total of 24 patients (34.2%). Based on the outcome, most of the research subjects recovered with a total of 67 patients (Table 1).

Table 1. Characteristics of research subjects

Characteristic	n (%)=70	Median (min-max)
Gender		
Male	31(44.3)	-
Female	39(55.7)	-
Age (years)		
21-40	27(38.6)	31(21-40)
41-60	40(57.1)	51(41-60)
>60	3(4.3)	65(61-65)
Comorbid		
No	51(72.9)	-
Yes		
DM	9(12.7)	-
NHS	3(4.3)	-
HT	3(4.3)	-
CKD	2(2.3)	-
Pulmonary TB	2(2.9)	-
Disease severity		
Mild	24(34.2)	-
Moderate	23(32.9)	-
Severe	23(32.9)	-
Outcome		
Recovery	67(95.7)	-
Death	3(4.3)	-

Source: Primary data

The basic characteristics of this study showed that there was a higher number of female patients than male patients with a total of 39 patients (55.7%). This was different from a study by John *et al.*, which reported a higher incidence of COVID-19 in males in all age groups. This was also different from a study by Wei *et al.*, which reported that the most gender in COVID-19 patients was male (56.2%). It is generally known that females' biological characteristics are better at producing a stronger immune response in dealing with infections including viral infections compared to males. However, population data in Makassar City in 2020 showed 4.56 million female residents and 4.50 million male residents, leading to a higher number of female patients in this study compared to males.[11-13]

Based on the results of the study in Table 1, it was found that most research subjects were patients aged 41-60 years, with a total of 40 patients (57.1%). The results of this study were in accordance with a study conducted by Wei *et al.*, which reported that the average age of the COVID-19 group was 50 years. This is due to decreased immunity and organ function along with increased age.[12]

Based on the results of the study in Table 1, it was also found that research subjects were dominated with patients who did not have a history of comorbidities compared to patients who had comorbidities, patients with mild severity were compared to patients with severe severity, and patients who recovered compared to patients who passed away. This was in accordance with a study by Kangdra *et al.*, which found that 55.2% of patients had no history of comorbidities and 44.8% had comorbidities, 45.5% of patients had mild symptoms, 42.7% of patients had moderate symptoms and 11.8% of patients had severe symptoms. This result was also in accordance with data from the COVID-19 National Task Force in November 2020, which reported that 82.84% of cases resulted in recovery and 3.38% of cases resulted in death.[14,15]

Based on data in Table 2, Kruskal-Wallis test results showed that there was a significant difference in the median of LDH levels according to disease severity, with the highest median of LDL found in the severe COVID-19 group (291.0 U/L) and the lowest median of LDL was found in the mild COVID-19 group (101.00). U/L) with p-value < 0.001. This indicated that there was a significant difference between LDH levels in patients with mild COVID-19, moderate COVID-19, and severe COVID-19 (Figure 1).

Table 2. LDH levels according to on disease severity

Disease Severity	LDH (U/L)		p
	n=80	Median (min-max)	
Mild	24	101.00(74.00-156.00)	
Moderate	23	143.00(126.00-253.00)	<0.001*
Severe	23	291.00(177.00-655.00)	

*Kruskal-Wallis test

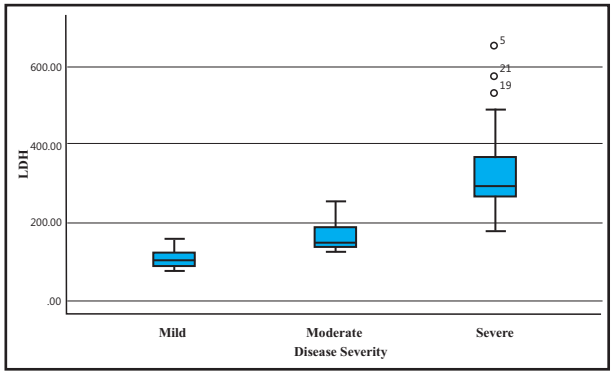


Figure 1. The difference in LDH levels according to disease severity

A correlation test was used to determine the relationship between LDH levels and disease severity. The results of the correlation test (Table 3) showed a very strong positive correlation between LDL levels and the severity of the disease (r=0.914, p<0.001). This suggested that higher LDH levels indicated a more severe COVID-19.

Table 3. Correlation test of LDH levels according to disease severity

Disease Severity	LDH (U/L)		p
	n=80	r	
Mild	24		
Moderate	23	0.914	<0.001*
Severe	23		

*Spearman correlation test

A strong positive correlation (r=0.914, p<0.001) in this study indicated that a more severe COVID-19 symptom is characterized by higher LDH levels in the blood. About 34.2% of patients with mild pain, 32.9% of patients with moderate pain, and 32.9% of patients with severe pain had median LDH levels of 101.00 U/L, 143.00 U/L, and 291.00 U/L, respectively, which was statistically significant (p<0.001). This was in accordance with a study by Li *et al.* in 26 patients with severe conditions and 43 patients with mild conditions, which found similar results; increased LDH levels were reported in severe patients with a median value of 247 U/L, while the median LDH levels in patients with the mild disease were 197 U/L.

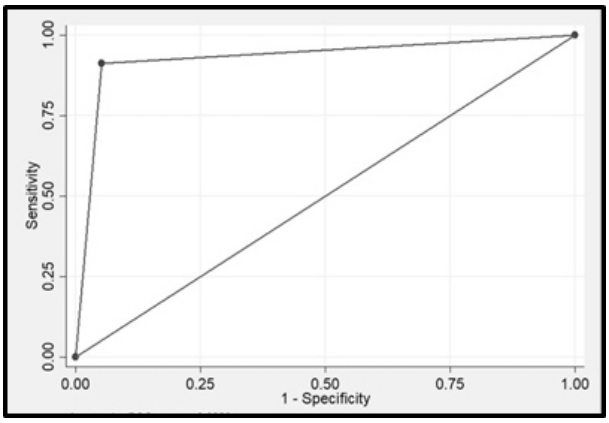
This was also in line with a study by Huang *et al.*, which found higher LDH levels in patients with severe conditions compared to patients with mild conditions, indicating that tissue damage plays an important role in the development of mild to severe disease.[10,14]

Lactate dehydrogenase is an intracellular enzyme, which is found in almost all the cytoplasm of body tissues and will be detected after damage to the tissue. The SARS-CoV-2 virus has a cytopathic effect and weakens the immune system thereby determining the severity of infection and tissue damage caused by an exaggerated immune response. There was no significant increase in proinflammatory chemokines and cytokines in patients with mild symptoms of COVID-19, in contrast with patients with severe symptoms. In this setting, it is found that there is a delay in the secretion of cytokines and chemokines by innate immune cells due to blockade by nonstructural viral proteins. Furthermore, this leads to a spike in proinflammatory cytokines and chemokines (IL-6, TNF-, IL-8, MCP-1, IL-1β, CCL2, CCL5, and interferon) through activation of macrophages and lymphocytes. The release of these cytokines triggers the activation of adaptive immune cells such as T cells, neutrophils, and NK cells, along with the continued production of proinflammatory cytokines. This rapid surge of proinflammatory cytokines triggers inflammation in the tissues that causes tissue damage and increases LDH levels. This damage can eventually result in ARDS and multi-organ failure which can lead to death in a short time.[16-22]

The cut-off value of LDH was determined by using ROC curve analysis at mild to moderate-severe degrees to determine whether LDH could be used as a marker of severity. Based on the Area Under Curve (AUC), the cut-off value of LDH was 0.930 ($p<0.001$), indicating that LDH can be used as a marker of the severity of COVID-19 disease.

Based on the ROC curve, the cut-off value of LDH >250.5 U/L was considered to have the highest level of sensitivity and specificity, with a sensitivity of 91.3%, specificity of 94.7%, PPV of 87.5%, NPV of 96.4% and accuracy of 91.3% (Graph 1).

This study showed that LDH can be a marker of the severity of COVID-19 patients with an AUC value of 0.930 ($p<0.001$) with an LDH cut-off value >250.5 U/L (sensitivity of 91.3%; specificity of 94.7%, NPV of 96.40%, NPV of 96.40%, and the accuracy of 91.30%. This was in line with a study by Rizal *et al.*, which suggested that the LDH cut-off value of 240-255 U/L can be a predictor of severity and mortality in COVID-19 patients. This study was also supported by



Graph 1. ROC curve of LDH according to disease severity

a study by Jin *et al.*, which reported an AUC value of 0.799 and LDH cut-off value > 240 U/L (sensitivity of 67.3%, specificity of 87.7%, PPV of 68.6%, and NPV of 81.25%) can be used as a predictor of COVID-19 severity. This indicated that LDH levels can be a marker of COVID-19 severity.[23-25]

These findings indicated that LDH at the beginning of hospital admission can be a strong marker of severity in COVID-19 patients. In addition, LDH levels are also one of the markers of tissue damage that are routinely tested and are widely available in almost all hospitals.

CONCLUSIONS AND SUGGESTIONS

There was a significant difference between LDH levels in patients with mild COVID-19, moderate COVID-19, and severe COVID-19 with a very strong positive correlation between LDH levels and the severity of the disease, suggesting that higher LDH levels indicate a more severe COVID-19 disease. Lactate dehydrogenase levels can be used as a marker of the severity of COVID-19 patients, thus enabling the identification of worsening patient conditions and proper selection of strategies for managing COVID-19 patients with wide availability and good economic value.

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