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Relationship between LDH Levels with COVID-19 Degree of Severity

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ABSTRACT

Background: LDH has proved to be a significant predictor for prognosis and follow-up in COVID-19 patients. Several studies report elevated LDH in hospitalized COVID-19 patients to be associated with a higher risk of death. Increased LDH levels can result from any tissue damage due to SARS-CoV-2 infection. The study aims to describe the relationship between LDH levels with COVID-19 19 degree of severity.

Methods: This study is a cross-sectional study of 55 patients who confirmed positive by RT-PCR SARS-CoV-2 at H. Adam Malik General Hospital Medan (November 2021 – Maret 2022). Examination of the LDH level was carried out by the Chemiluminescent Immunoassays method (Abbott Architect). COVID-19 degree of severity was assessed based on the diagnostic criteria for COVID-19 cases in Indonesia.

Results: Among the 55 COVID-19 patients in this study, the average age found was 45.73, with men 54.5%. Moderate, severe, and critical patients were found in 63.6%; 29.1%; and 7.3% respectively. The mean LDH level at admission was 278 U/L, higher in the severe (333.19 U/L) and critical (465.75 U/L) groups compared to the moderate (231.31 U/L) groups. Increased LDH ≥ 256 U/L proved to be related to COVID-19 degree of severity upon hospital admission (CI 95%; p = 0.001).

Conclusions: LDH levels that increased ≥ 256 U/L were significantly related to COVID-19 degree of severity during hospital admission.

Keywords: COVID-19 Degree of Severity, LDH

ABSTRAK

Latar Belakang: LDH telah terbukti menjadi prediktor signifikan untuk prognosis dan tindak lanjut pada pasien COVID-19. Beberapa penelitian melaporkan peningkatan LDH pada pasien COVID-19 yang dirawat di rumah sakit dikaitkan dengan risiko kematian yang lebih tinggi. Peningkatan kadar LDH dapat terjadi akibat kerusakan jaringan akibat infeksi SARS-

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CoV-2. Penelitian ini bertujuan untuk mendeskripsikan hubungan kadar LDH dengan tingkat keparahan COVID-19.

Metode: Penelitian ini merupakan penelitian potong lintang terhadap 55 pasien yang terkonfirmasi positif RT-PCR SARS-CoV-2 di Rumah Sakit Umum H. Adam Malik Medan (November 2021 – Maret 2022). Pemeriksaan kadar LDH dilakukan dengan metode Chemiluminescent Immunoassays (Abbott Architect). Tingkat keparahan COVID-19 dinilai berdasarkan kriteria diagnostik untuk kasus COVID-19 di Indonesia.

Hasil: Di antara 55 pasien COVID-19 dalam penelitian ini, usia rata-rata yang ditemukan adalah 45,73, dengan pria 54,5%. Pasien sedang, berat, dan kritis ditemukan pada 63,6%; 29.1%; dan 7,3% masing-masing. Tingkat LDH rata-rata saat masuk adalah 278 U / L, lebih tinggi pada kelompok berat (333,19 U / L) dan kritis (465,75 U / L) dibandingkan dengan kelompok sedang (231,31 U / L). Peningkatan LDH ≥ 256 U/L terbukti terkait dengan tingkat keparahan COVID-19 saat masuk rumah sakit (CI 95%; p = 0,001).

Kesimpulan: Tingkat LDH yang meningkat ≥ 256 U/L secara signifikan terkait dengan tingkat keparahan COVID-19 selama masuk rumah sakit.

Kata kunci: Tingkat keparahan COVID-19, LDH

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1 Introduction

SARS-CoV-2, commonly called Covid-19 is a virus that spread widely to the entire world throughout 2020. SARS-CoV itself is not a new virus, its previous type has been identified and successfully controlled. However, the mutation that occurred caused its infectious rate to increase and until now the world agreed that the ground zero of SARS CoV 2 is the city of Wuhan, located in mainland China.[1]

After SARS CoV-2 was successfully identified, many researchers have conducted studies to find out more about the structure and nature of the virus. It is important to control its spread and also to determine the therapy and prognosis of the patient. One of the laboratory parameters that was researched is Lactate Dehydrogenase (LDH). In theory, LDH is an enzyme which had a role as a biomarker of hypoxia and tissue damage in the body. Therefore, several studies have been carried out to connect LDH levels with the severity of Covid-19 patients. This follows the hypothesis that when SARS CoV-2 infection in the body worsens, inflammation of tissue occurs which results in hypoxia and massive destruction of lung tissue, which would result in increased LDH levels.[2,3,4]

Previous studies have found that increased LDH levels > 6 times in COVID-19 patients are related to degree of severity. Meanwhile, other studies by Han, et al and Dong X prove that LDH can be a specific marker for Covid-19 degree of severity.[5,6,7]

LDH as a prognosis factor was also successfully proved to be significant by Tjahyadi RM, Poggiali E, and Li C. Severity degree and prognosis of COVID-19 patients were proved to be in line with high levels of LDH in patients. The significance that the research proved is enough to make LDH an independent risk factor for determining the good and bad prognosis of a COVID-

19 patient. Of course, it is necessary to trace the patient's comorbidities to avoid false positives where LDH can increase due to other diseases.[8,9,10] The purpose of this study was to determine the relationship between LDH levels and COVID-19 patients' degree of severity at H. Adam Malik Hospital in Medan.

2 Method

The research type is analytic and the design used is cross-sectional. Blood samples from 55 COVID-19 patients during the period November 2021 – March 2022 at H. Adam Malik Hospital in Medan were taken to assess their LDH levels. The type of sample required for LDH examination is serum, venous blood from the patient will be taken using a syringe and then processed into serum. The patient's serum will be analyzed using the *Abbott Architect Analyzer* for his/her LDH levels. The research was conducted after obtaining approval for ethical clearance from the Research Committee for Health Sector, Faculty of Medicine, Universitas Sumatra Utara / RSUP H. Adam Malik Medan. All patients who were willing to participate in this study were provided with informed consent in written form, either signed by him/herself or signed by their family members. In giving such consent, the patient has been informed of the meaning, benefits, and possible unpleasant side effects that may occur during the research.

3 Result

The subjects were mostly male which numbered 30 people (54.5%). The average age of the subjects was 45.73 years with the youngest age being 18 years and the oldest aged 81 years. A total of 16 subjects (29.1%) had a history of hypertension and 9 subjects (16.4%) had a history of DM. From the results of the COVID-19 degree of severity examination, most of the 35 people (63.6%) were on moderate severity, followed by severe patients with 16 people (29.1%). (Tabel 1).

Table 1 Characteristics of the Research Subjects

Subject Characteristics	**n = 55**
Sex, n (%)	
Male	30 (54.5)
Female	25 (45.5)
Age, y.o	
Mean (SD)	45.73 (16.93)
Median (Min – Mak)	45 (18 – 81)
Hypertension, n (%)	
With	16 (29.1)
Without	39 (70.9)
DM, n (%)	
With	9 (16.4)
Without	46 (83.6)
Covid-19 Degree of Severity, n (%)	
Moderate	35 (63.6)
Severe	16 (29.1)
Critical	4 (7.3)

Table 2, it appears that the LDH levels of all subjects involved in this study. The average LDH level was 278 U/L (SD = 159.1 U/L) with the lowest level of 111 U/L and the highest level of 875 U/L.

Table 2 LDH Levels in Covid-19 Patients

LDH Levels, U/L	**n = 55**
Mean (SD)	278 (159.1)
Median (Min-Max)	219 (111 – 875)

In Table 3, there is a relationship between LDH levels and COVID-19 degree of severity. In subjects with moderate severity, 35 people showed LDH levels with an average of 231.31 U/L (SD = 132.69 U/L). In subjects with severe severity, 16 people showed LDH levels with an average of 333.19 U / L (SD = 132.08 U / L). In subjects with critical severity, 4 people showed LDH levels with an average of 465.75 U / L (SD = 283.13 U / L). Using the Kruskal Wallis test, it was shown that there was a significant relationship between LDH levels and the COVID-19 patient's degree of severity (p = 0.005).

Table 3 Relationship of LDH Levels with Covid-19 Degree of Severity

Covid-19 Degree of Severity	n	LDH Levels, ng/mL		p*
		Mean (SD)	Median (Min-Max)	
Moderate	35	231.31 (132.69)	178 (111-605)	0.005
Severe	16	333.19 (132.08)	340.5 (124-583)	
Critical	4	465.75 (283.13)	382.5 (223-875)	

*Kruskal Wallis

To get the AUC value from LDH, the categorization of the severity of COVID-19 is divided into two categories. Namely, moderate degrees totaling 35 people and severe-critical degrees totaling 20 people.

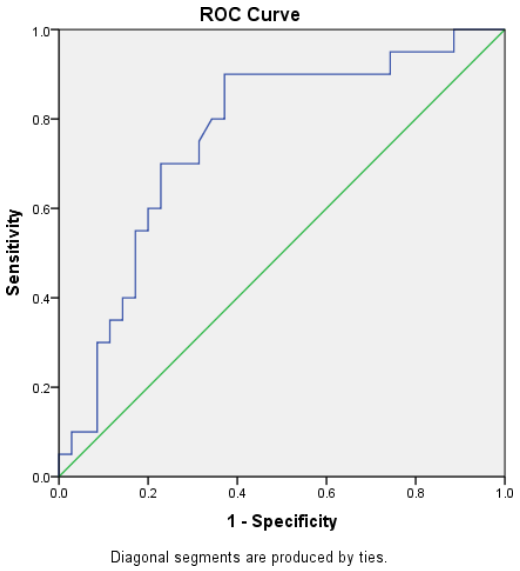

Table 4 Accuracy of LDH Value in Predicting Covid-19 Degree of Severity

LDH	Degree of Severity		Sensitivity	Specificity	PPV	NPV
	Severe & Critical	Moderate				
≥ 256 U/L	14	8	70%	77,1%	63,6%	81,8%
< 256 U/L	6	27				

By using the LDH cut-off value of 256 U / L to predict the severity of COVID-19, sensitivity, and specificity values were obtained by 70% and 77.1%, respectively, with positive presumption values of 63.6% and negative suspect values of 81.8%, the accuracy of LDH values was 74.6%.

Table 5 Relationship of LDH Levels, DM, and Hypertension to Covid-19 Degree of Severity

Variable	Covid-19 Degree of Severity		p	PR
	Severe and Critical	Moderate		95%IK
LDH Levels				
≥ 256 U/L	14 (63.6)	8 (36.4)	0.001[a]	3.500
< 256 U/L	6 (18.2)	27 (81.8)		1.589-7.710
DM, n (%)				
With	7 (77.8)	2 (22.2)	0.008[b]	2.752
Without	13 (28.3)	33 (71.7)		1.544-4.905
Hypertension, n (%)				
With	10 (62.5)	6 (37.5)	0.010[a]	2.438
Without	10 (25.6)	29 (74.4)		1.265-4.695

[a]Chi Square, [Fischer's] Exact

Of the 22 subjects with LDH levels ≥ 256 U/L, there were 14 people (63.6%) with severe and critical degrees. Meanwhile, of the 33 subjects with LDH levels < 256 U/L only 6 people (18.2%) with severe and critical degrees. Using the Chi-Square test showed that there was a significant relationship between LDH levels and the degree of severity of COVID-19 ($p < 0.001$) and the Prevalence Ratio value of 3.500 (95%IK = 1.589-7.710). The value of RP = 3.500 indicates that subjects with LDH levels ≥ 256 U/L will tend to be at risk of severe and critical degrees by 3.500 times compared to subjects with LDH levels < 256 U/L.

Of the 9 subjects with DM, there were 7 people (77.8%) with severe and critical degrees. Meanwhile, of the 46 subjects who did not have DM, there were 13 people (28.3%) with severe and critical degrees. Fischer's Exact test showed that there was a significant relationship between DM and the severity of Covid-19 ($p = 0.008$) with a Prevalence Ratio value of 2.752 (95%IK = 1.544- 4.905). The value of PR = 2.752 indicates that subjects with DM will tend to be at risk of severe and critical degrees by 2.752 times compared to subjects who do not have hypertension.

Of the 16 subjects with Hypertension, there were 10 people (62.5%) with severe and critical degrees. Meanwhile, of the 39 subjects who did not have Hypertension, there were 13 people (28.3%) with severe and critical degrees. Using the Chi-Square test, it showed that there was a significant relationship between Hypertension and the severity of Covid-19 ($p = 0.010$) with a Prevalence Ratio value of 2.483 (95%IK = 1.265-4.695). A value of PR = 2.483 indicates that subjects with Hypertension will tend to be at risk of severe and critical degrees by 2.483 times compared to subjects who do not have Hypertension.

Table 6 Multivariate Analysis of the Relationship between LDH Levels, DM, and Hypertension to Covid-19 Degree of Severity

Variable	B	p	Exp(B)	95% C, I, for EXP(B)	
				Lower	Upper
Selection I					
LDH	2.692	0.003	14.767	2.538	85.926
DM	0.297	0.723	1.345	0.261	6.940
Hypertension	2.005	0.090	7.428	0.733	75.266
Constant	-2.821	0.001	0.060		
Selection II					
LDH	2.738	0.002	15.461	2.720	87.873
Hypertension	2.211	0.034	9.127	1.179	70.660
Constant	-2.785	0.001	0.062		

By using the enter method, issuing each independent variable starting from the variable with the highest p-value> 0.05, it was obtained that only two independent variables significantly affected the severity of COVID-19 in this study, namely the LDH level (p = 0.002) and Hypertension (p = 0.034).

The most dominant variable influencing the severity of COVID-19 is the LDH level with the largest Exp (B) value of 15.461 (95% IK = 2.720 – 87.873) meaning that COVID-19 sufferers with LDH levels ≥ 256 U / L will tend to be at risk of experiencing severe and critical Covid-19 severity by 15.461 times greater than subjects with LDH levels < 256 U / L.

4 Discussion

This research is a cross-sectional study that aims to determine the role of LDH levels in assessing the severity degree of COVID-19 disease. This research was conducted at the Department of Clinical Pathology and in the Department of Pulmonology, H. Adam Malik General Hospital in Medan using consecutive sampling on confirmed COVID-19 patients by using PCR upon their hospitalization starting from November 2021 to March 2022. Of the 55 patients, 54.5% were male and 45.5% were female. The average age of sufferers is 45.73 years. This is in line with previous research by Isbaniah in Jakarta and Guan Wu in Wuhan where the majority of Covid-19 patients are men.[11,12]

Based on the results of laboratory examinations, in Table 4.2, the average value of LDH levels of 278 U / L. This figure is lower than the results of research by Dong X in 2020 with a figure of 353.5 U / L, but by several studies from the meta-analysis by Martha JW in 2020. LDH results in line with previous studies show that this study is by the initial theory that Covid-19 increases LDH levels along with the severity degree of the disease.[5,8,13] This study found that the relationship between LDH levels and COVID-19 degree of severity had a significant relationship,

as stated in table 4.4, LDH levels ≥ 256 U/L could be used as predictors of severity degree. This study resulted in a sensitivity value of 70% and a specificity of 77,1%, this is in line with the previous research conducted by Dong X where the sensitivity obtained was 94.4%, with a specificity of 89.2%.[5]

In cases of severe infections such as COVID-19, damaged tissue triggers an increase in cytokine production, resulting in the release of large amounts of LDH into the bloodstream. Therefore, a significant increase in LDH can be found in patients with COVID-19 infection, although the amount of elevation will be dependent on the organ damage that occurs in the patient. In this regard, comorbid diseases like Hypertension and DM in COVID-19 patients will theoretically result in a worse prognosis compared to other patients who do not have the condition.

Based on a meta-analysis by Martha JW, researchers wanted to assess comorbid factors in COVID-19 patients, namely DM and hypertension. As discussed in the literature review, comorbidities in COVID-19 patients worsen the patient's prognosis and are more at risk of causing tissue damage. In theory, comorbid factors increase the severity of Covid-19. After the enter method was carried out, an independent variable that had a significant effect on the severity of COVID-19 was hypertension.[13]

Based on the discussion of the results of the study above, it is concluded that LDH levels can be used as a reference to determine the COVID-19 patient's degree of severity, especially with a value of ≥ 256 U/L. This is by the basic theory that infectious diseases that cause tissue damage to organs will increase the release of LDH into blood circulation, this theory is also supported by previous studies.[5,8,13] The study has some limitations, there may be some statistical bias due to the small sample size. Therefore, more research is still needed for a better understanding of the disease. Severe infections can lead to tissue damage and the release of LDH through cytokine-mediated mechanisms.[14] In the case of severe COVID-19 infections, patients with interstitial pneumonia progressing to acute respiratory distress syndrome often release higher amounts of LDH into the bloodstream. LDH, specifically isozyme 3 found in lung tissue, is implicated in this process. However, the specific contribution of different LDH isoenzymes to the observed LDH elevation in COVID-19 remains unknown. Moreover, LDH levels are also increased in thrombotic microangiopathy, which is associated with renal failure and myocardial injury.[15,16] Reports have indicated elevated levels of D-dimer and thrombocytopenia in severe COVID-19 patients, suggesting that a hypercoagulable state may contribute to the severity of illness and mortality.[17,18].

5 Conclusion

Based on the results of data analysis obtained in this study, it can be concluded that LDH levels are significantly related to COVID-19 degree of severity. Tingkat LDH rata-rata saat masuk

adalah 278 U / L, lebih tinggi dari kelompok berat dan kritis dibandingkan dengan kelompok sedang. Peningkatan LDH ≥ 256 U/L terbukti terkait dengan tingkat keparahan COVID-19 saat masuk rumah sakit.

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