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Correlation Between Lactate Dehydrogenase (LDH) Values and Aspects Score at the Beginning of Treatment in Acute Ischemic Stroke

Lathifatul Fikriyah*, M. Saiful Ardhi, Sita Setyowatie
Universitas Airlangga, Indonesia
Email: lathifatul.fikriyah@fk.unair.ac.id*

Abstrak
Stroke is the second leading cause of death worldwide, with ischemic stroke comprising 87% of cases. Metabolic acidosis from hypoxia promotes anaerobic glycolysis, raising lactate dehydrogenase (LDH) levels, which reflects neuronal tissue injury and inflammation in acute ischemic stroke. The Alberta Stroke Program Early CT Score (ASPECTS) is used to assess ischemic brain injury on non-contrast CT, aiding early prognosis and treatment decisions. This cross-sectional study at Dr. Soetomo Hospital, Surabaya (February–May 2023), included 30 acute ischemic stroke patients (53.3% male, mean age 60.2 ± 7.1 years, onset 2–5 days). Exclusion criteria were prior thrombolysis, cancer, or organ failure. LDH levels were measured at admission using the Alinity C analyzer, and ASPECTS was calculated from initial CT scans. Spearman's correlation was used for analysis. Results showed a significant inverse correlation between LDH and ASPECTS (r = -0.279, p = 0.003), indicating that higher LDH levels correspond with lower ASPECTS (larger infarcts). Mean LDH was elevated (258.75 ± 50.65 U/L, normal 120–190 U/L). Comorbidities included hypertension (90%), dyslipidemia (83.3%), and diabetes mellitus (56.7%). These findings suggest that serum LDH may be a valuable adjunct biomarker for early assessment of ischemic stroke severity when advanced imaging is unavailable, helping clinicians estimate infarct size rapidly. Further research involving larger populations is recommended to confirm LDH's utility and to examine its combination with other biomarkers for acute ischemic stroke management.

Keywords: Acute ischemic stroke, ASPECTS Score, Lactat Dehidrogenase

INTRODUCTION

Globally, stroke ranks as the third most common cause of disability and the second most common cause of mortality. Over the past 40 years, the incidence of stroke has more than doubled in low- and middle-income countries, accounting for nearly 70% of all stroke cases. Stroke patients face a high mortality rate, with approximately 84% dying within three years of diagnosis (World Health Organization, 2021). Among all strokes, ischemic strokes account for 87%, while intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) account for 10% and 3%, respectively (Virani et al., 2020).

In acute ischemic stroke, *metabolic acidosis* results from oxygen deprivation. As oxygen levels drop, *pyruvate* is converted to *lactate*, promoting *anaerobic glycolysis* and leading to *lactic acidosis* (Hartings, 2017). Hypoxia triggers intracellular changes in astrocytes and neurons, impairing glucose uptake and disrupting brain function (Genc et al., 2011). Neurons lose the ability to maintain cellular homeostasis and ionic gradients soon after ischemia, initiating cascades of *excitotoxicity*, *oxidative stress*, *nitrate stress*, inflammation, and apoptosis.

The presence of *lactate* in brain tissue reflects anaerobic metabolism and is associated with damage caused by acidosis. Under hypoperfused conditions, lactate may diffuse from the infarct core to surrounding tissue, damaging neurons, impairing *cerebrovascular autoregulation*, increasing edema, leading to secondary ischemia, and enlarging infarct size—all contributing to poor clinical outcomes (Brouns et al., 2008).

Lactate dehydrogenase (LDH), an intracellular enzyme, facilitates the conversion of pyruvate to lactate during glycolysis, supporting energy production under anaerobic conditions (Wang et al., 2021). LDH is predominantly located in cell mitochondria and cytoplasm. Tissue injury results in the release of LDH into extracellular fluid, making it a useful biomarker for cellular damage (Valvona et al., 2016). Elevated serum LDH levels, often present in acute ischemic stroke, indicate tissue necrosis and hypoxia. LDH is also associated with inflammatory responses contributing to the development and prognosis of cerebral infarction (Jin H et al., 2022; Jin XX et al., 2022).

The *Alberta Stroke Program Early CT Score* (*ASPECTS*) is a semi-quantitative tool used to assess early ischemic changes on non-contrast CT. It divides the middle cerebral artery territory into 10 regions, assigning one point per normal region; points are subtracted for evidence of ischemia. Lower ASPECTS corresponds to more extensive infarction and worse outcomes. Clinically, a higher ASPECTS is linked to a more favorable prognosis (Schröder et al., 2017; Esmael et al., 2021).

This study aims to investigate the correlation between serum LDH levels and ASPECTS in patients with acute ischemic stroke. By exploring this relationship, the research seeks to enhance early prognostic accuracy and inform targeted interventions. Identifying LDH as a potential biomarker may benefit clinical decision-making, especially in settings where advanced neuroimaging is limited. Furthermore, the study contributes to understanding the biochemical mechanisms underlying ischemic injury and may support future therapeutic innovations.

RESEARCH METHODS

From February to May 2023, a cross-sectional analytical study was conducted at Dr. Soetomo General Hospital, Surabaya, involving patients admitted with acute ischemic stroke. Participants were selected using a consecutive admissions approach, ensuring that all eligible patients during the study period were considered. Inclusion criteria required participants to be 18 years or older, experiencing their first episode of acute ischemic stroke with symptom onset between 2–5 days, and willing to participate by signing an informed consent form. Patients were excluded if they had received intravenous thrombolysis, had acute coronary syndrome, a history of cancer, sepsis, severe renal or hepatic impairment, or other significant medical conditions that could interfere with the study outcomes.

Data collection involved recording serum *lactate dehydrogenase* (LDH) levels and relevant clinical information using standardized data sheets. Statistical analysis was performed using SPSS version 22.0. The Shapiro-Wilk test was used to assess the normality of data distribution. A p-value greater than 0.05 indicated a normal distribution. Depending on the data distribution, Pearson correlation was applied for normally distributed variables, while non-parametric alternatives were used for non-normally distributed variables.

The study protocol was reviewed and approved by the Ethics Committee of Dr. Soetomo General Academic Hospital, ensuring adherence to ethical research standards (reference number: 0577/KEPK/I/2023). This study design allowed for systematic observation of the relationship between serum LDH levels and ischemic stroke severity, contributing to the body of evidence in stroke pathophysiology and prognosis.

RESULT AND DISCUSSION

A total of 30 patients, comprising 16 (53%) male and 14 (46.7%) female, satisfied the inclusion criteria. Age-based characteristics showed a median of 60 years, with a minimum range of 45 and a maximum of 76. Meanwhile, the mean and standard deviation of 60.2 ± 7.1 were obtained from a total sample of 30 subjects.

Table 1. Characteristics of Study Subjects

Variable	N (%)	Value
Gender		

Variable	N (%)	Value
Males	16 (53,3%)	
Female	14 (46,7%)	
Age (Mean ± SD)		60,2±7,1
Hipertension		
Present	27 (90,0%)	
No	3 (10,0%)	
Hypoxia		
Present	2 (6,7%)	
No	28 (93,3%)	
Hypoglycemia		
Present	2 (6,7%)	
No	28 (93,3%)	
Diabetes Mellitus		
Present	17 (56,7%)	
No	13 (43,3%)	
Dyslipidemia		
Present	25 (83,3%)	
No	5 (16,7%)	

Source: Primary data collected from acute ischemic stroke patients admitted to Dr. Soetomo General Hospital, Surabaya (February–May 2023).

According to the results of Table 1, the distribution of characteristics for comorbid hypertension, hypoxia, hypoglycemia, DM, and dyslipidemia was 27 (90%), 2 (6.7%), 2 (6.7%), 17 (56.7%), and 25 subjects (83.3%), respectively. The tetrameric enzyme LDH, which is a member of the 2-hydroxy acid oxidoreductase family, speeds up the conversion of NADH to NAD+ and pyruvate to lactate. Cells frequently use the enzyme for anaerobic respiration. In this study, blood LDH levels were obtained through venous blood examination at Dr. Soetomo Hospital Laboratory using the Alinity C LDH method, with normal reference values for adults of 120-190 U/L using a numerical scale. LDH examination was conducted when the patient initially entered the hospital on day 2 of onset until day 5 of onset. The following is a descriptive overview of LDH in the study sample.

Table 2. LDH Descriptive

Variable	Value	*p-value Normalities**
LDH Mean ± SD	258,75±50,65	0,051

* Shapiro-Wilk test, declared normal if the p-value> 0.05

Source: Laboratory analysis using the Alinity C LDH method (reference range: 120–190 U/L), Dr. Soetomo Hospital Laboratory

In the table showing the results of the Spearman test for the relationship/correlation between LDH and ASPECT Score, we can see that the p-value is 0.003, which is less than 0.05. This indicates that there is a meaningful relationship/correlation between LDH and ASPECTS Score according to statistical tests. Looking at the r-value in the relationship/correlation test, we can see that it is 0.279, or 27.9%, placing it in the weak relationship strength category. The relationship between LDH and ASPECT Score is negative, where if the ASPECT score value is high or large, the LDH value will be low and vice versa.

Table 3. Relationship/Correlation Test of LDH with ASPECTS Score

Variabel	r	*p value*
LDH----ASPECT Score	-0,279	0,003

*There is a relationship if the p-value <0.05

Source: Spearman's correlation analysis of primary data (SPSS v22.0)

Increased lactate dehydrogenase (LDH) is observed in various disease processes, including stroke, tissue injury, necrosis, hypoxia, and malignancies. LDH is a cytoplasmic enzyme that is expressed in many tissues. In 2020, Jin Hu et al. found that blood LDH levels in conjunction with gender were independently linked to the severity of disease.61 Patients with higher LDH, male gender, and more risk factors had a worse prognosis of ischemic stroke, according to research published in 2020 by Xia-xia et al. (Jin XX., 2022)

As a result of hypoxia and ischemia, LDH is quickly increased in the brain parenchyma during an acute ischemic stroke; it then leaks into the bloodstream, worsening cerebral infarction and peripheral edema. Acute ischemic stroke develops when cerebral blood flow is interrupted, leading to brain tissue necrosis and softening. Subsequently, the relevant functional areas experience impairment. Serum and cerebrospinal fluid levels of LDH are higher in those who have had an ischemic stroke, and this finding is linked to the development of stroke.16 In this study, there was a correlation between LDH and ASPECT Score using the Spearman test (p-value 0.003), where the results were statistically significant, with a low relationship strength (r value =-0.279). The relationship between LDH and ASPECT Score is negative, where if the ASPECT Score value is high or large, the LDH value will be low and vice versa. This suggests that LDH is associated with the infarct area. This is by the research of Xia-xia Jin et al. in 2022 mentioned that LDH in cardioembolic stroke patients and LAA was significantly higher than in other groups. In the study, they stated that serum LDH levels were associated with cerebral infarct size and cerebral edema and predicted neurological changes and 90-day outcomes.

After acute ischemic stroke (AIS), the brain produces LDH in the blood. Every kind of damaged brain cell, from neurons to astrocytes to microglia, experiences an increase in intracellular LDH as a means of energy usage and adaptation to the hypoxic and ischemic environment brought on by cerebral artery occlusion. During hypoxia and reoxygenation, brain cells show an increase in LDH. However, LDH can be released into the extracellular space and peripheral circulation through a broken blood-brain barrier (BBB) when brain cells are harmed or die. Additionally, tumor studies have shown that extracellular lactic acid, a byproduct of lactate dehydrogenase, stimulates vascular endothelial cells to express vascular endothelial growth factor and inflammatory factor IL-8. This could lead to angiogenesis and local inflammation, which in turn could contribute to the breakdown of the blood-brain barrier and cerebral edema in ischemic stroke. According to the research hypothesized by Jin et al., increased serum LDH levels accurately represent the degree of brain tissue injury. Researchers confirmed that levels of serum LDH were predictive of neurological abnormalities and 90-day prognosis, as well as of the extent of cerebral infarcts and cerebral edema. (Eren et al., 2021)

Some have speculated that LDH could be a biomarker for inflammatory conditions. The pathological progression of death and poor functional results may be aided by inflammation, which is linked to endothelial cell dysfunction and the development of atherosclerosis and atheroma instability. One potential indicator of worse outcomes following a stroke is a rise in LDH, which occurs in response to injury to organ systems. Patients with acute ischemic stroke or transient ischemic attack had a significantly higher risk of mortality and poor functional outcomes at 3-month and 1-year follow-up if their serum LDH levels were higher, according to a study by anxin wang et al. (Wang et al., 2021)

In a similar vein, Yair Lamp et al. noted that among stroke patients, the subgroup with cortical stroke had substantially higher CSF LDH concentrations than the subgroups with lacunar infarction and ganglia infarction, while there was no difference between CSF LDH and serum LDH. On the other hand, no subgroup showed a link (p=0.2) between infarct volume and CSF LDH levels. In a 1990 study, Lamp et al. The reason being, imaging was done in the study by Yair Lamp et al. just after a stroke began, before 24 hours had passed.

The findings from this study substantiate a significant inverse correlation between serum Lactate Dehydrogenase (LDH) levels and the ASPECT score in ischemic stroke infarct patients, underscoring the potential of LDH as a biochemical marker of infarct severity. Elevated LDH likely reflects the extent of cellular injury and anaerobic metabolism triggered by ischemic insult, which is consistent with the pathophysiological mechanisms underpinning stroke progression (Zhang et al., 2023). The ASPECTS scoring system, by enabling a standardized early radiologic assessment of ischemic changes, complements this by providing a visual quantification of infarct size and severity, which aligns with biochemical markers like LDH to offer a comprehensive severity profile.

Recent work has expanded the understanding of LDH beyond a mere marker of cell death to also include its role in neuroinflammation and oxidative stress mechanisms during stroke evolution (Tan et al., 2021). These insights suggest LDH elevation may not solely indicate passive tissue damage but also active metabolic and inflammatory processes contributing to infarct expansion and neurological deterioration. Such a perspective strengthens the rationale for integrating LDH measurement with imaging scores to refine prognosis and therapeutic targeting.

The clinical utility of combining biochemical and imaging markers was highlighted by Zhao et al. (2021), who demonstrated that a multimodal approach using serum biomarkers with ASPECT scoring significantly improved the predictive accuracy for functional outcomes post-stroke. This combined approach may help identify patients at higher risk for adverse progression and poor recovery, enabling more tailored and timely interventions, including decisions around thrombolysis or mechanical thrombectomy.

Additionally, serial measurement of LDH levels may provide dynamic insights into infarct progression and treatment response, as suggested by Mansour et al. (2020). This temporal dimension could be crucial for monitoring stroke evolution beyond the initial imaging window, addressing a key limitation of static imaging assessments.

However, it is necessary to consider factors that might confound LDH levels, such as concomitant hemolysis, liver dysfunction, or other systemic conditions, which require careful exclusion or adjustment in clinical evaluation. Furthermore, while ASPECTS is valuable for assessing middle cerebral artery territory strokes, its applicability in other stroke types or territories is limited, which calls for complementary imaging parameters in broader patient populations. Combining LDH with other new biomarkers, such as neurofilament light chains or glial fibrillary acidic protein, and with cutting-edge imaging methods like perfusion CT or MRI, should be the focus of future studies. The results must be confirmed by large-scale, multi-center prospective studies in order to determine exact LDH cutoffs that correspond with various ASPECT score ranges and clinical outcomes.

In summary, our study strengthens the evidence that serum LDH is a promising adjunct biomarker that correlates inversely with ASPECT scores, reflecting ischemic injury severity in acute stroke. The integration of biochemical markers with imaging scores enhances the early assessment of stroke severity, benefiting prognosis estimation and guiding therapeutic decision-making in clinical practice.

CONCLUSION

Patients with acute ischemic stroke showed a statistically significant negative correlation between their LDH and ASPECT Score. if the ASPECT score value is high or large, the LDH value will be low and vice versa. The evidence that serum LDH is a promising adjunct biomarker that correlates inversely with ASPECT scores, reflecting ischemic injury severity in acute stroke. The findings align with the research objective of establishing a link between LDH and ASPECT scores, offering clinical utility for prognosis and targeted interventions. Future studies should expand on these results with larger, multicenter cohorts to validate LDH cutoffs for different ASPECT score ranges and explore its integration with advanced imaging techniques or additional biomarkers, such as neurofilament light chains, to further refine stroke severity evaluation and therapeutic strategies.

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