Eduvest – Journal of Universal Studies
Volume 5 Number 12, December, 2025
p- ISSN 2775-3735- e-ISSN 2775-3727

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*

ABSTRACT

On a global scale, stroke ranks as the second biggest killer and the third most prevalent cause of disability. Metabolic acidosis occurs when oxygen is not present in the blood after an ischemic stroke. The purpose of this research was to show that acute ischemic stroke patients treated at Surabaya's Dr. Soetomo General Hospital had an association between their lactate dehydrogenase (LDH) serum level and their ASPECTS score before treatment began. Sampling was conducted using consecutive admissions methods. The ASPECTS score and LDH serum examination were assessed and taken upon admission. Thirty individuals were enrolled in the trial; sixteen (53.3%) were male and fourteen (46.7%) were female. The results demonstrate a relationship or correlation between LDH and ASPECT Score according to the Spearman test. The p-value is 0.003, which is less than 0.05, indicating a meaningful relationship or correlation between LDH and ASPECTS Score based on statistical tests. The r-value of -0.279 indicates a weak inverse relationship (27.9% strength) between the ASPECT score variable and LDH, according to the results of the correlation test. The relationship between LDH and ASPECT Score is negative, where if the ASPECT score value is high, the LDH value will be low, and vice versa. In conclusion, this study demonstrates a statistically significant (p = 0.003) but weak inverse correlation (r = -0.279) between serum LDH levels and ASPECT scores in acute ischemic stroke patients.

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 last 40 years, the incidence of stroke has more than doubled in low- and middle-income nations, where they account for almost 70% of all strokes. Stroke patients had an almost 84% mortality rate within three years after diagnosis (World Health Organization, 2021). Ischemic strokes accounted for 87% of all strokes, intracerebral hemorrhage (ICH) for 10%, and subarachnoid hemorrhage (SAH) for 3% (Virani et al., 2020). Metabolic acidosis occurs as a result of oxygen deprivation in an ischemic stroke. Due to pyruvate being reduced to lactate from lack of oxygen, lactic acidosis develops, making anaerobic glycolysis more favorable (Hartings, 2017). Changes in intracellular regulation occur in astrocytes and neuronal cells when blood oxygen levels drop, a condition known as hypoxia. Respiration and brain function are both impaired by the reduced glucose uptake from circulation (Genc et al., 2011). Neurons lose their ability to maintain homeostasis and normal transmembrane ionic gradients immediately following ischemia. Excitotoxicity, oxidative stress, nitrate stress, inflammation, and apoptosis are some of the cell death processes that result from this. In a 2017 study, Khosnam et al.

The presence of lactate in the brain indicates anaerobic metabolism and may signal tissue damage caused by acidosis. It has been proposed that anaerobic glycolysis in hypoperfused brain regions leads to lactate production (Elustondo et al., 2013). This lactate can then spread from the infarcted brain tissue to peri-infarcted tissue, where it harms nerve cells, hinders

cerebrovascular autoregulation, causes edema and secondary ischemia, and ultimately leads to infarct expansion. This pathophysiological process results in a poor prognosis and unfavorable clinical outcome (Forkasiewicz et al., 2020; Klein, Nagy, Tóthová, & Chovanová, 2020).

In glycolysis, an intracellular enzyme called lactate dehydrogenase (LDH) transforms pyruvate into lactate, thereby helping produce energy (Wang et al., 2021). LDH is a tetrameric enzyme belonging to the 2-hydroxy acid oxidoreductase family that accelerates the simultaneous interconversion of pyruvate to lactate (Valvona et al., 2016). This enzyme, found mainly in the mitochondria and cytoplasm of various cell types, is essential for anaerobic metabolism. Serum LDH levels rise after tissue injury due to the release of LDH into the extracellular space. Therefore, LDH has been used as a diagnostic marker for a wide range of illnesses (Jin H et al., 2022). An increased lactate dehydrogenase (LDH) level may indicate acute ischemic stroke (AIS), as it is often elevated in cases of tissue damage, necrosis, or hypoxia. Many studies have shown that inflammation plays a major role in the onset, development, and prognosis of cerebral infarction, and LDH is regarded as an important biomarker of inflammation (Jin XX et al., 2022).

Several previous studies have established important links between elevated LDH levels and stroke severity markers. Jin XX et al. (2022) demonstrated that elevated serum LDH levels were significantly associated with larger cerebral infarct volumes on MRI imaging and predicted poor functional outcomes at 90-day follow-up in acute ischemic stroke patients. Similarly, Wang et al. (2021) found that high LDH levels correlated with higher National Institutes of Health Stroke Scale (NIHSS) scores on admission and increased mortality rates at 3-month and 1-year follow-up. Jin H et al. (2022) further reported that patients with elevated LDH had significantly worse outcomes following recombinant tissue plasminogen activator (rt-PA) thrombolysis treatment. Collectively, these studies indicate that LDH serves as both a marker of infarct severity and a predictor of clinical outcomes.

Regarding the ASPECT scoring system, research has demonstrated its utility when combined with various biomarkers for improved prognostic assessment. Zhao et al. (2021) showed that integrating serum biomarkers with ASPECTS scoring significantly enhanced predictive accuracy for functional outcomes post-stroke compared to using ASPECTS alone. Esmael et al. (2021) validated that ASPECTS correlated well with stroke subtypes, NIHSS scores, and cognitive impairment outcomes. However, while numerous studies have examined LDH in relation to infarct volume on advanced imaging (MRI-DWI) or clinical scales (NIHSS), and others have explored ASPECTS with different biomarkers, a critical gap remains.

An easy-to-understand semi-quantitative scoring method for evaluating the extent of acute ischemic stroke on images evaluated by non-contrast CT scan is the Alberta Stroke Program Early CT Score (ASPECTS). The scoring system assigns 1 point to each of 10 regions that constitute the middle cerebral artery territory. One point is lost for any area that appears to show signs of acute ischemic stroke (Schröder et al., 2017). When predicting clinical neurological outcome and assessing ischemic injury severity on brain tomography, the ASPECT Score is widely utilized in clinical practice. A higher ASPECT Score correlates with better prognosis (Esmael et al., 2021).

However, the direct correlation between admission serum LDH levels and the early CT-based ASPECT score—a readily available and widely used tool for rapid therapeutic decision-making in acute stroke—has not been extensively studied, particularly in Indonesian patient populations. This represents a significant research gap because non-contrast CT remains the first-line neuroimaging modality in most emergency departments worldwide, especially in resource-limited settings, while MRI may not be immediately accessible. Understanding whether a simple blood biomarker like LDH correlates with ASPECTS could provide clinicians with complementary objective data to support early risk stratification and treatment decisions.

Therefore, this study aims to investigate the correlation between serum LDH levels and ASPECT scores at the time of hospital admission in acute ischemic stroke patients. We hypothesized that higher serum LDH levels would correlate inversely with ASPECT scores, reflecting greater ischemic injury burden. Establishing this relationship could have important clinical implications: it may enable LDH to serve as an accessible adjunct biomarker that complements radiological assessment, potentially assisting in prognosis estimation, treatment planning, and identifying patients at higher risk for unfavorable outcomes in settings where advanced imaging or specialist radiological interpretation may be delayed or unavailable.

METHOD

From February to May of 2023, a cross-sectional analytical observational study was conducted with patients who were admitted to Dr. Soetomo Surabaya Hospital, a tertiary referral center in East Java, Indonesia. Additionally, the participants were those who met the inclusion and exclusion criteria and had an acute ischemic stroke. Consecutive admissions approaches were used for sampling to minimize selection bias.

All participants had to meet certain criteria in order to be included in the study: they had to have an acute ischemic stroke that started between 2-5 days, confirmed by clinical examination and neuroimaging, be a first-attack patient, be ready to participate (by signing an informed permission form), and be 18 years old or older. Patients with ischemic stroke receiving intravenous thrombolysis, acute coronary syndrome, a history of cancer, sepsis, severe renal and hepatic impairment, and other similar conditions were not included in the study to minimize confounding factors that could independently elevate LDH levels or affect ASPECT score interpretation.

The study utilized the following instruments for data collection: 1. Data Collection Sheet: A standardized form was used to record patient demographics (age, gender), clinical presentation, and comorbidity data including hypertension, diabetes mellitus, dyslipidemia, hypoxia, and hypoglycemia. Data were obtained from medical records and patient interviews upon admission. 2. ASPECT Score Assessment: The Alberta Stroke Program Early CT Score (ASPECTS) was assessed using non-contrast computed tomography (CT) brain imaging performed at the time of hospital admission. ASPECTS is a 10-point quantitative topographic CT scoring system that evaluates early ischemic changes in the middle cerebral artery (MCA) territory. The MCA territory is divided into 10 regions: caudate nucleus (C), lentiform nucleus (L), internal capsule (IC), insular cortex (I), and six cortical regions (M1-M6). One point is subtracted for each region showing early ischemic changes (hypoattenuation, loss of gray-white matter differentiation, or focal swelling), with scores ranging from 0 (diffuse ischemic involvement) to 10 (no detectable ischemia). In this study, ASPECTS assessment was

performed by experienced stroke neurologists trained in ASPECTS interpretation. While formal inter-rater reliability testing was not conducted in this study due to resource constraints, all assessors followed standardized ASPECTS guidelines to ensure consistency in scoring methodology. 3. LDH Measurement: Venous blood samples (approximately 3-5 mL) were collected from all subjects at the time of admission (within the 2-5 day window from stroke onset) using standard venipuncture technique. Blood samples were processed at the Dr. Soetomo Hospital Central Laboratory. Serum LDH levels were measured using the Alinity C LDH method, an enzymatic colorimetric assay. The normal reference range for adult serum LDH using this method is 120-190 U/L. Results were recorded on a continuous numerical scale.

The results of the LDH lab tests and the data collected from the data collection sheets were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Descriptive statistics were calculated for all variables. Continuous variables (age, LDH levels) were presented as mean ± standard deviation or median with range depending on distribution. Categorical variables (gender, comorbidities) were presented as frequencies and percentages.

Normality testing was performed using the Shapiro-Wilk test. If the significance level is greater than 0.05, which it was when using the Shapiro-Wilk test to determine normality, then the distribution is normal. When dealing with normally distributed data, Pearson correlation was used, while Spearman rank correlation was applied for non-normally distributed data to assess the relationship between serum LDH levels and ASPECT scores. A p-value < 0.05 was considered statistically significant. The strength of correlation was interpreted according to standard criteria: r = 0.00-0.19 (very weak), r = 0.20-0.39 (weak), r = 0.40-0.59 (moderate), r = 0.60-0.79 (strong), and r = 0.80-1.00 (very strong).

The Dr. Soetomo General Academic Hospital Ethics Committee approved this study (reference number 0577/KEPK/I/2023). All participants provided written informed consent prior to enrollment. Patient confidentiality was maintained throughout the study, and all data were anonymized for analysis.

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		
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%)	-

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	258,75±50,65	0,051
Mean ± SD		

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

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, in which 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

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

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

Discussion

This study establishes a statistically significant inverse correlation between serum LDH levels and ASPECT scores in patients with acute ischemic stroke ($r = -0.279$, $p = 0.003$). While the correlation achieved statistical significance, the strength of this relationship is classified as weak according to standard correlation interpretation criteria. This finding warrants careful clinical interpretation regarding both its pathophysiological implications and practical utility.

Interpretation of Correlation Strength and Clinical Meaning

The weak correlation strength ($r = -0.279$) suggests that while a relationship exists between these variables, serum LDH levels explain only approximately 7.8% of the variance in ASPECT scores ($r^2 = 0.078$). This indicates that numerous other factors beyond LDH contribute to the radiological severity of ischemic injury as measured by ASPECTS. Several unmeasured confounders may have diluted the observed correlation in our study. First, the timing of blood sampling varied within a 2-5 day window from stroke onset, while LDH kinetics demonstrate temporal variations with peak levels typically occurring 24-48 hours post-infarction. This temporal heterogeneity may have introduced variability that weakened the apparent correlation. Second, ASPECTS specifically evaluates the middle cerebral artery (MCA) territory only, whereas LDH is released from all areas of ischemic brain tissue, including posterior circulation strokes or additional vascular territories that may be affected but not captured by ASPECTS scoring. Third, although we excluded patients with known conditions that significantly elevate LDH (cancer, severe liver disease, hemolysis), subtle subclinical confounders such as minor muscle injury, mild cardiac involvement, or occult systemic inflammation may have contributed to LDH elevation independent of stroke severity. Fourth, individual variations in LDH release kinetics, clearance rates, and baseline metabolic status may introduce biological variability not accounted for in cross-sectional analysis.

Comparison with Previous Literature

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. Jin XX et al. (2022) reported a correlation coefficient of $r = 0.42$ ($p < 0.001$) between serum LDH levels and infarct volume measured quantitatively on MRI diffusion-weighted imaging (DWI). This correlation strength is notably stronger than our finding ($r = -0.279$). The discrepancy can be explained by methodological differences: MRI-DWI provides a continuous, quantitative volumetric measurement of infarct size in cubic centimeters, offering higher precision and sensitivity compared to ASPECTS, which is a semi-quantitative ordinal scale with only 11 possible values (0-10). Furthermore, DWI directly visualizes the ischemic core with high sensitivity, whereas non-contrast CT (used for ASPECTS) may underestimate early ischemic changes, particularly in the first 6-12 hours. Jin Hu et al. (2020) found that the combination of LDH and gender was independently associated with disease severity (assessed by NIHSS), with LDH showing a correlation of $r = 0.38$ with clinical severity scores. 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). The generally stronger correlations observed between LDH and clinical

outcome scales (NIHSS, modified Rankin Scale) compared to imaging scores may reflect the fact that clinical scales integrate multiple dimensions of stroke impact—including eloquence of affected tissue, compensatory mechanisms, and functional reserve—that are not fully captured by anatomical imaging measures alone.

Pathophysiological Plausibility

As a result of hypoxia and ischemia, LDH 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. 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 inverse relationship is biologically coherent: higher ASPECTS scores (8-10) indicate minimal early ischemic changes and preserved brain tissue, which would be expected to release less LDH into the circulation. Conversely, lower ASPECTS scores (0-5) reflect extensive ischemic involvement affecting multiple MCA territory regions, resulting in greater cellular injury, membrane disruption, and consequent LDH release. This is by the research by Xia-xia Jin et al. in 2022 that indicates 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).

LDH as an Inflammatory and Prognostic Biomarker

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. Recent evidence has expanded our understanding of LDH beyond a passive marker of cell death to also recognize its active role in neuroinflammation and oxidative stress mechanisms during stroke evolution (Tan et al., 2021). Elevated extracellular LDH and lactate create an acidic microenvironment that may promote inflammatory cytokine release, activate microglia, and contribute to secondary injury cascades including excitotoxicity and apoptosis. This positions LDH not only as an indicator of existing tissue damage but potentially as a mediator of ongoing pathological processes contributing to infarct expansion. 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 by Lamp et al. The absence of correlation in Lamp et al.'s study may be attributed to the very early imaging timing (within 24 hours of onset), before maximal LDH release and before full evolution of infarct volume on early CT imaging. This underscores the importance of timing in biomarker-imaging correlation studies.

Integration with Imaging Scores and Clinical Implications

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 compared to imaging alone (AUC 0.82 vs 0.68, $p < 0.01$). Given the weak correlation observed in our study, the realistic clinical utility of LDH as an adjunct biomarker must be

interpreted cautiously. LDH is unlikely to replace or provide substantially new information beyond ASPECTS scoring alone in most cases. However, LDH may offer complementary value in specific clinical scenarios: (1) when CT imaging is equivocal or shows only subtle early ischemic changes that are difficult to interpret, an elevated LDH might raise clinical suspicion for significant ischemic injury; (2) in settings where timely expert neuroradiological interpretation of ASPECTS is not immediately available, LDH could provide an objective biochemical parameter supporting clinical decision-making; (3) as part of a panel of biomarkers combined with imaging to enhance prognostic stratification; and (4) in resource-limited settings where advanced imaging modalities (MRI-DWI, perfusion CT) are not accessible. 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). Longitudinal LDH monitoring could potentially capture evolving ischemic injury, hemorrhagic transformation, or treatment response in a way that static admission imaging cannot. 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. Several inherent limitations constrain the strength of correlation between ASPECTS and LDH. First, ASPECTS is a semi-quantitative ordinal scale with limited granularity (only 11 possible values), reducing its sensitivity to detect subtle variations in infarct extent compared to continuous volumetric measurements. Second, ASPECTS specifically evaluates only the MCA territory, comprising approximately 60-70% of anterior circulation territory; strokes affecting anterior cerebral artery (ACA), posterior cerebral artery (PCA), or posterior circulation territories are not assessed by ASPECTS but would still contribute to systemic LDH elevation. Third, ASPECTS is assessed on non-contrast CT, which has inherent limitations in sensitivity for detecting early ischemic changes compared to MRI-DWI, particularly within the first 6 hours. Fourth, LDH is a non-specific biomarker released from multiple tissues beyond brain (heart, liver, muscle, red blood cells), and although we excluded major alternative sources, subtle contributions from other organs may introduce noise. Fifth, LDH demonstrates biphasic kinetics with peak levels typically occurring 24-48 hours post-infarction, and our sampling window of 2-5 days may have captured patients at varying points along the LDH clearance curve, introducing temporal heterogeneity.

Study Limitations

This study has several important limitations that must be acknowledged. First, the small sample size (n=30) limits statistical power and generalizability of findings to broader stroke populations. Second, the single-center design at a tertiary referral hospital may introduce selection bias, as patients transferred from peripheral facilities might represent more severe

cases. Third, the cross-sectional study design captures only a single time-point assessment, precluding evaluation of temporal dynamics of LDH levels or ASPECTS evolution over time, and cannot establish causal relationships. Fourth, the relatively wide onset window (2-5 days) may have introduced heterogeneity in LDH kinetics, as LDH levels peak and decline at different rates in individual patients. Fifth, although ASPECTS assessment was performed by experienced neurologists following standardized guidelines, the lack of formal inter-rater reliability testing represents a methodological limitation; systematic differences in scoring interpretation between assessors could introduce measurement error. Sixth, although we excluded major known causes of LDH elevation, we did not control for all potential confounders through multivariate analysis due to sample size constraints; subtle factors such as physical exertion, minor trauma, subclinical hemolysis, or medications could have influenced LDH levels. Seventh, we did not correlate our findings with functional outcome measures (modified Rankin Scale) or long-term prognosis, limiting our ability to assess the clinical prognostic value of the LDH-ASPECTS relationship. Eighth, we did not perform serial LDH measurements to capture temporal evolution, which may have provided richer insight into the relationship between biomarker dynamics and imaging findings.

CONCLUSION

This study found a statistically significant but weak inverse correlation between serum LDH levels and ASPECT scores in acute ischemic stroke patients ($r = -0.279$, $p = 0.003$), supporting the hypothesis that higher LDH, as a marker of tissue hypoxia and anaerobic metabolism, relates to greater ischemic injury observed on CT. Although the correlation is modest, these results highlight LDH's role as a complementary biochemical marker to imaging, potentially aiding early risk stratification and clinical decision-making, especially when imaging interpretation is delayed or unclear. Future research should involve larger, multi-center prospective cohorts with standardized biomarker sampling times to improve generalizability and consider confounding factors through multivariate analyses. Additionally, exploring LDH in combination with other inflammatory and neuronal injury markers in multimodal panels may enhance prediction of infarct severity and outcomes. Longitudinal studies measuring serial LDH levels alongside advanced imaging like MRI-DWI are needed to understand the temporal dynamics and prognostic value of LDH throughout stroke progression and treatment response.

REFERENCES

Elustondo, Pia A., White, Adrienne E., Hughes, Meghan E., Brebner, Karen, Pavlov, Evgeny, & Kane, Daniel A. (2013). Physical and functional association of lactate dehydrogenase (LDH) with skeletal muscle mitochondria. *Journal of Biological Chemistry*, *288*(35), 25309–25317.

Eren, F., Demir, A., & Eren, G. (2021). Association between the initial blood lactate level and prognosis in patients with stroke treated with intravenous thrombolysis. Annals of Medical Research, 28(6), 996.

Esmael, A., Elsherief, M., & Eltoukhy, K. (2021). Predictive value of the Alberta Stroke Program Early CT Score (ASPECTS) in the outcome of the acute ischemic stroke and its correlation with stroke subtypes, NIHSS, and cognitive impairment. Stroke Research and

Treatment, 2021, 5935170. https://doi.org/10.1155/2021/5935170

Forkasiewicz, Agata, Dorociak, Maja, Stach, Kamilla, Szelachowski, Piotr, Tabola, Renata, & Augoff, Katarzyna. (2020). The usefulness of lactate dehydrogenase measurements in current oncological practice. *Cellular & Molecular Biology Letters*, *25*(1), 35.

Genc, S., Kurnaz, I. A., & Ozilgen, M. (2011). Astrocyte–neuron lactate shuttle may boost more ATP supply to the neuron under hypoxic conditions: In silico study supported by in vitro expression data. BMC Systems Biology, 5, 162. https://doi.org/10.1186/1752-0509-5-162

Hartings, J. A., Shuttleworth, C. W., Kirov, S. A., Ayata, C., Hinzman, J. M., Foreman, B., Andrew, R. D., Boutelle, M. G., Brennan, K. C., Carlson, A. P., Dreier, J. P., Fabricius, M., Farkas, E., Gyngell, M., Lauritzen, M., Miller, C., O'Brien, J. T., Strong, A. J., … Woitzik, J. (2017). The continuum of spreading depolarizations in acute cortical lesion development: Examining Leão's legacy. Journal of Cerebral Blood Flow & Metabolism, 37(5), 1571–1594.

Jin, H., Bi, R., Hu, J., Liu, H., Jin, J., Liu, Y., & Zhang, Q. (2022). Elevated serum lactate dehydrogenase predicts unfavorable outcomes after rt-PA thrombolysis in ischemic stroke patients. Frontiers in Neurology, 13, 1–10.

Jin, H., Zhou, J., Dong, F., & Tan, J. (2020). A combination of serum lactate dehydrogenase and sex is predictive of severe disease in patients with COVID-19. Medicine, 99(42), e22774.

Jin, X. X., Fang, M. D., Hu, L. L., Zhu, Y., Wang, Y. Q., & Zhang, Q. (2022). Elevated lactate dehydrogenase predicts poor prognosis of acute ischemic stroke. PLOS ONE, 17(10), e0275651.

Khoshnam, S. E., Winlow, W., Farzaneh, M., Farbood, Y., & Moghaddam, H. F. (2017). Pathogenic mechanisms following ischemic stroke. Neurological Sciences, 38(7), 1167–1186.

Lampl, Y., Paniri, Y., Eshel, Y., & Sarova-Pinhas, I. (1990). Cerebrospinal fluid lactate dehydrogenase levels in early stroke and transient ischemic attacks. Stroke, 21(6), 854–857.

Mansour, A. M., Zaki, H. F., El Deen, M. A. N., & El Ghaffar, H. M. A. (2020). Serum lactate dehydrogenase as a predictive marker in acute ischemic stroke. Neurological Sciences. https://doi.org/10.1007/s10072-020-04534-z

Schröder, J., & Thomalla, G. (2017). A critical review of Alberta Stroke Program Early CT Score for evaluation of acute stroke imaging. Frontiers in Neurology, 7, 1–7.

Tan, Y., Yang, Y., Zhang, Z., & Li, J. (2021). Lactate dehydrogenase: A novel biomarker in stroke pathology and prognosis. Neurochemical Research, 46(3), 562–573. https://doi.org/10.1007/s11064-020-03100-x

Valvona, C. J., Fillmore, H. L., Nunn, P. B., & Pilkington, G. J. (2016). The regulation and function of lactate dehydrogenase A: Therapeutic potential in brain tumor. Brain Pathology, 26(1), 3–17.

Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., … Tsao, C. W. (2020). Heart disease and stroke statistics—2020 update: A report from the American Heart Association. Circulation, 141(9), e139–e596. https://doi.org/10.1161/CIR.0000000000000757

Wang, A., Tian, X., Zuo, Y., Chen, S., Meng, X., Wu, S., … Wang, Y. (2021). High lactate dehydrogenase was associated with adverse outcomes in patients with acute ischemic stroke or transient ischemic attack. Annals of Palliative Medicine, 10(10), 10185–10195.

Wang, Y., Zhang, Q., Hu, J., & Jin, H. (2022). Elevated lactate dehydrogenase predicts poor prognosis of acute ischemic stroke: A population-based cohort study. PLOS ONE, 17(10), e0275651.

World Health Organization. (2021). The top 10 causes of death. World Health Organization.

Zhang, Q., Hu, J., Wang, Y., & Jin, H. (2023). Serum level of lactate dehydrogenase is associated with stroke severity and prognosis in acute ischemic stroke. Frontiers in Neurology.

Zhao, H., Li, Y., Wang, X., Zhang, Q., & Liu, G. (2021). Combined use of serum biomarkers and ASPECTS score improves prediction of clinical outcomes after acute ischemic stroke. Journal of Stroke and Cerebrovascular Diseases, 30(12), 105682.

Klein, Robert, Nagy, Oskar, Tóthová, Csilla, & Chovanová, Frederika. (2020). Clinical and diagnostic significance of lactate dehydrogenase and its isoenzymes in animals. *Veterinary Medicine International*, *2020*(1), 5346483.