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Correlation Between Lactate Dehydrogenase Levels and National Institutes of Health Stroke Scale Scores at the Onset of Acute Ischemic Stroke

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Abstract

Background: In acute ischemic stroke, reduced oxygen supply may trigger metabolic acidosis and cellular injury. Lactate dehydrogenase (LDH), as an intracellular enzyme, helps generate energy by converting pyruvate to lactate in glycolysis. This study aimed to examine the correlation between serum LDH levels and the National Institutes of Health Stroke Scale (NIHSS) score at the onset of treatment among patients with acute ischemic stroke.

Methods: This analytical observational study used cross-sectional design, involving patients with acute ischemic stroke hospitalized at Dr. Soetomo Surabaya Hospital, Indonesia, between February and May 2023. Participants were selected using consecutive sampling. Serum LDH levels and NIHSS score were measured upon admission. The correlation between LDH levels and NIHSS score was analyzed using the Spearman test, with statistical significance set at $p<0.05$.

Results: A total of 30 patients were included, of whom 16 (53.3%) were male. A significant correlation was found between LDH levels and NIHSS scores ($p=0.001$). The correlation coefficient ($r=0.785$) indicated a strong positive correlation between serum LDH levels and stroke severity.

Conclusions: This study demonstrates a strong positive correlation between LDH levels and NIHSS scores at the onset of acute ischemic stroke treatment. These findings suggest that LDH may serve as a practical early biomarker for assessing stroke severity. Integrating LDH measurement into initial evaluation may facilitate faster risk stratification and support timely clinical decision-making. Further studies with larger sample sizes are needed to validate its prognostic role in routine practice.

Keywords: Acute ischemic stroke, lactate dehydrogenase, National Institutes of Health Stroke Scale (NIHSS)

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Introduction

Stroke risk increases significantly with advancing age due to vascular aging, inflammation, and metabolic disturbances.[1] Older adults tend to experience more severe strokes and poorer functional outcomes.[2] Recognizing age-related changes is essential for targeted prevention and management. Current guidelines emphasize the need for early risk factor control and individualized care to promote healthy aging and reduce future stroke burden.[3]

Globally, stroke ranks third among the leading contributors to disability and is the second major cause of mortality. Approximately 70% of strokes cases occur in low- and middle-income countries, where incidence has continued to rise over the past four decades.[4] Nearly 84% of stroke patients die within three years of diagnosis.[5] In Indonesia, according to data from the World Health Organization (WHO), stroke has been the leading cause of death between 2000 and 2019.[6]

Acute ischemic stroke results in decreased cerebral oxygen supply, leading to metabolic

acidosis. Under hypoxic condition, cells shift from aerobic metabolism to anaerobic glycolysis, converting pyruvate to lactate and causing lactic acidosis.[6] Hypoxia alters intracellular regulatory mechanisms within astrocytes and neurons. Decreased glucose delivery from the bloodstream to the brain impairs cellular respiration and leads to diminished brain function.[7] The failure of ischemic neurons to maintain ionic gradients disrupts cellular homeostasis, which triggering excitotoxicity, oxidative and nitrosative stress, inflammation, and apoptosis.[8]

Lactate is widely recognized as a biomarker of anaerobic metabolism in the brain and is also considered a potential indicator of tissue injury due to acidosis. Increased lactate production reflects anaerobic glycolysis in hypoperfused brain regions, and diffusion from the infarct core to peri-infarct tissue may damage cerebrovascular autoregulation, increase cerebral edema, and enlarge the infarct size. These processes contribute to unfavorable clinical outcomes and poor prognosis.[9] On the other hand, the astrocyte–neuron lactate shuttle (ANLS) theory suggests that lactate produced by astrocytes may serve as an alternative energy substrate for neurons during metabolic stress.[10] Astrocyte-produced lactate supports neuronal excitability, plasticity, memory integration, and neural homeostasis.[11] Experimental study also demonstrates neuroprotective effects of lactate in ischemic brain tissue on neural tissue, according to animal.[12] A clinical study has reported correlation between lactate levels and stroke severity, stating that higher lactate concentrations correlate with poorer neurological status.[13]

Lactate dehydrogenase (LDH) plays a central role in the metabolic process. LDH is an intracellular tetrameric enzyme that catalyzes the reversible conversion of pyruvate to lactate during anaerobic glycolysis.[14–15] LDH is mostly found in the cytoplasm and mitochondria of various tissues. Serum LDH levels rise when cellular injury causes enzyme release into the extracellular space. LDH is therefore considered as a nonspecific biomarker of tissue damage and prognosis across multiple clinical conditions.[16] In acute ischemic stroke (AIS), elevated LDH levels are commonly associated with tissue hypoxia, necrosis, and inflammation. LDH has been proposed as a potential indicator of the severity and progression of cerebral infarction.[17] Given the metabolic role of LDH and its association with cellular injury, investigating its association with neurological impairment may provide clinically relevant insight. Therefore, this study aimed to analyze the relationship between serum LDH levels and functional status, as measured by the National Institutes of Health Stroke Scale (NIHSS) in patients with acute ischemic stroke at the onset of treatment.

Methods

This analytical observational study used a cross-sectional design involving patients diagnosed with acute ischemic stroke who were hospitalized at Dr. Soetomo Surabaya Hospital, Indonesia, between February and May 2023. Patients were selected using consecutive sampling methods. Inclusion criteria were adults aged ≥18 years experiencing a first-attack acute ischemic stroke with an onset of 2–5 days, and who were willing to participate by signing an informed consent.

Informed consent was obtained according to institutional ethics regulations and the Declaration of Helsinki. Decision-making capacity was assessed at admission. Patients who were fully conscious and capable of understand the study information signed the informed consent form personally. For patients with motor deficits that prevented writing, consent was provided through a mark, assisted signature, or verbal agreement witnessed and documented by the research team, whereas the patients with impaired consciousness, severe aphasia, or cognitive limitations, consent was obtained from a legally authorized representative, such as spouse or first-degree family member. Patients were excluded if they had acute coronary syndrome, a history of malignancy, sepsis, severe hepatic or renal impairment, or if they were ischemic stroke patients receiving thrombolysis IV therapy.

The minimum required sample size was calculated using a standard correlational analysis formula, applying a significance level of 0.05, statistical power of 80%, and an expected correlation coefficient of 0.5. This resulted in a sample size requirements of 30 subjects, in accordance with recommended guidelines for sample estimation in correlation studies.[18]

Blood LDH levels were obtained through venous blood sampling and analyzed at Dr. Soetomo Hospital Laboratory using the Alinity C LDH method, with adults' reference values of 120–190 U/L. LDH examinations were conducted upon admission, between day 2 and day 5 after stroke onset. Stroke severity was assessed using the National Institutes

of Health Stroke Scale (NIHSS) at the time of admission.

Data obtained were analyzed using SPSS software version 22.0. The Shapiro-Wilk test was applied to assses data normality. Pearson correlation was used for normally distributed variables, whereas for non-normally distributed variables, Spearman's rank correlation was applied. Because NIHSS values were not normally distributed, the relationship between LDH levels and NIHSS scores was assessed using the Spearman correlation test, with statistical significance set at $p<0.05$. Ethical approval for this study was granted by the Ethics Committee of Dr. Soetomo General Academic Hospital (Reference number 0577/KEPK/I/2023).

Results

A total of 30 patients participated in the study, consisting of 16 males (53.3%) and 14 females (46.7%). The median age was 60 years (range: 45 to 76 years) and the mean age was 60.2±7.1 years. Hypertension was the most prevalent comorbidity (90%), followed by dyslipidemia (83.3%), diabetes mellitus (DM) (56.7%) hypoxia (6.7%) and hypoglycemia (6.7%) (Table 1).

The normality test indicated that LDH levels were normally distributed (p=0.051), with a mean value of 258.75±50.65. Furthermore, there were no meaningful differences in LDH distribution between males (r=0.719, p=0.001) and females (r=0.724, p=0.001). In contrast, NIHSS score were normally distributed (p=0.001). The NIHSS scores ranged from 4 to 18, with a median of 7.00 (Table 2).

Overall, analysis using the Spearman correlation test demonstrated a strong positive correlation between LDH and NIHSS scores (r=0.785, p=0.001), indicating that higher LDH levels were associated with greater stroke severity (Figure 1).

Discussion

This study has demonstrated a significant positive correlation between serum LDH levels and NIHSS scores in patients with acute

Table 1 Characteristics of Patients with Acute Ischemic Stroke Hospitalized at Dr. Soetomo Hospital, Surabaya (February–May 2023)

Variable	n (%)
Gender	
Male	16 (53.3)
Female	14 (46.7)
Age (mean ± SD) years	60.2±7.1
Hypertension	
Present	27 (90.0)
Not present	3 (10.0)
Hypoxia	
Present	2 (6.7)
Not present	28 (93.3)
Hypoglycemia	
Present	2 (6.7)
Not present	28 (93.3)
Diabetes mellitus	
Present	17 (56.7)
Not present	13 (43.3)
Dyslipidemia	
Present	25 (83.3)
Not present	5 (16.7)

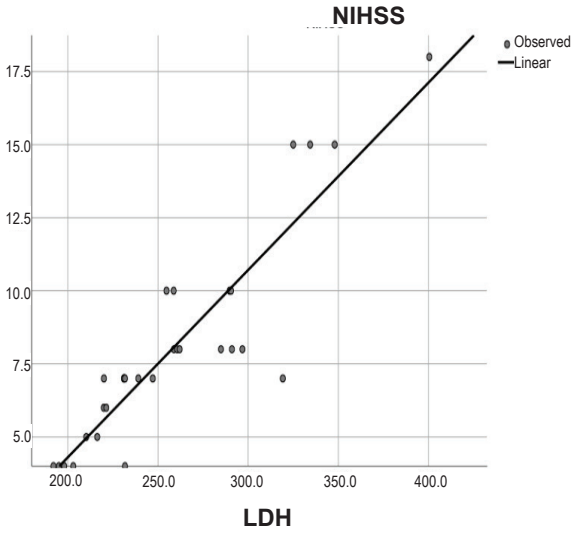

Figure 1 Correlation between Lactate Dehydrogenase (LDH) and National Institutes of Health Stroke Scale (NIHSS) Scores

Table 2 Correlation Between LDH and NIHSS by Gender

Gender	Variable	r	p-value*
Male	LDH-NIHSS	0.719	0.001
Female	LDH-NIHSS	0.724	0.001

Note: LDH= Lactate dehydrogenase, NIHSS= National Institutes of Health Stroke Scale,
*Correlation is significant at p<0.05

ischemic stroke. Higher LDH levels were associated with more severe neurological impairment, indicating that LDH reflects the extent of neuronal injury and metabolic stress caused by cerebral ischemia. These findings support the hypothesis that LDH may serve as an early biomarker of stroke severity and also align with growing interests in biomarkers associated with to aging-related metabolic vulnerability.[19]

LDH is an important enzyme in anaerobic glycolysis and is mostly found in the cytoplasm and mitochondria of various tissues, including the brain, heart, liver, and lungs.[20] Tissue injury leads to the release of LDH into the extracellular space and subsequently into the bloodstream. During an ischemic event, oxygen deprivation triggers anaerobic metabolism, resulting in increased LDH activity and lactate production. This metabolic shift is accompanied by neuronal energy failure, oxidative stress, and impaired cellular homeostasis, all of which contribute to ischemic tissue injury.[21,22]

In response to cerebral artery blockage, damaged neurons, astrocytes, and microglia may release LDH into the circulation, particularly when the blood-brain barrier (BBB) becomes compromised. Elevated LDH may also exacerbate cerebral injury, as a study has shown that lactate can stimulate inflammatory cytokine such as IL-8 and vascular endothelial growth factor (VEGF), potentially promoting angiogenesis and local inflammation, and BBB disruption.[18] This mechanism may explain the strong correlation between LDH levels and NIHSS score.

This study's results are consitents with previous research reporting that elevated blood LDH levels are associated with higher mortality and poorer functional outcome in acute ischemic stroke or transient ischemic attacks.[15,17] LDH therefore represents a potential predictor of disease severity and prognosis. In this study, the hypothesis that LDH correlates positively with baseline NIHSS scores was confirmed.

Importantly, the association between LDH levels and NIHSS severity also intersects with the biology of aging. Aging is characterized by "inflammaging," a chronic low-grade inflammatory state accompanied by oxidative stress and mithocondrial decline.[23,24] These processes reduce cellular resilience and exacerbate neurological injury following ischemic events. In addition, age-related vascular changes, including endothelial dysfunction, arterial stiffness, and impaired neurovascular coupling, contribute to larger infarct sizes and more severe neurological defisits.[24] Collectively, these mechanism may help explain why LDH levels tend to be more elevated and clinically informative in older individuals experiencing stroke.

From an anti-aging and preventive medicine perspective, LDH may function not only as an acute indicator of stroke severity but also as a surrogate marker of underlying metabolic and vascular aging. Interventions targeted at improving metabolic health and slowing vascular aging such as caloric restriction, regular physical activity, antioxidant strategies, and therapies supporting mitochondrial function have demonstrated beneficial effects on oxidative stress reduction and endothelial repair.[25,26] Optimizing these lifestyle and theurapeutic factors may theoretically reduce LDH elevation during ischemic events and improve neurological outcomes in older adults. Furthermore, combining LDH with other biomarkers such as neuron-specific enolase (NSE), S100B, or high-sensitivity C-reactive protein (hs-CRP), may enhance risk prediction models for both acute stroke and age-related vulnerability.[27]

However, this sudy has several limitations. LDH is not specific to stroke and may also be elevated in conditions such as hemolysis, hepatic injury, myocardial infarction, or malignancy, limiting its diagnostic specificity.[28,29] Additionally, only a single LDH measurement was taken, preventing assessment of temporal patterns that may reflect disease progression. Future research should investigate serial LDH measurements, explore combinations with other neurological biomarkers, and investigate whether LDH-guided interventions can improve clinical outcomes.

In conclusion, this study demonstrates a strong positive correlation between serum LDH levels and NIHSS score in patients with acute ischemic stroke. LDH reflects the degree of neuronal injury and metabolic stress, suggesting its value as a simple, assessible biomarker for early severity assessment. Given the interplay between ischemic injury, inflammation, and vascular aging, LDH may support risk stratification in older adults and contribute to broader efforts to enhance stroke prevention and healthy aging.

Authors' Contributions

LF conceptualized and designed the study, developed the research methodology, supervised the overall research process, interpreted the data, and drafted the

initial manuscript. SA conducted data collection and data curation, performed the statistical analysis, and contributed to data interpretation and critical revision of the manuscript. SS contributed to the study design and methodology, assisted with data analysis, and participated in revising the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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