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Serum Lactate Dehydrogenase Dynamics in Acute Ischemic and Hemorrhagic Stroke: A Marker of Prognosis but Not Diagnosis

Akut İskemik ve Hemorajik İnmede Serum Laktat Dehidrogenaz Dinamiği: Tanı Değil, Prognoz Belirteci

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ABSTRACT

Aim: Lactate dehydrogenase (LDH) is a marker of cellular damage, increasingly recognized for its prognostic value in stroke. However, its role in differentiating stroke types and in predicting outcomes remains incompletely defined.

Materials and Methods: In this retrospective, single-center study, 1,299 patients [1,185 acute ischemic stroke (AIS), 114 intracerebral hemorrhages (ICHs)] between 2018 and 2023 were analyzed. Admission and first-week LDH levels were compared across stroke types, etiologies, and outcomes. Functional status was assessed using the 3-month modified Rankin Scale (mRS). Multivariate stepwise linear regression was applied to determine factors independently associated with admission LDH.

Results: Mean admission LDH was 329.3±176.1 U/L in AIS and 342.4±174.9 U/L in ICH (p=0.45). First-week LDH levels were 276.2±148.1 U/L in AIS and 300.1±123 U/L in ICH (p=0.19). In AIS, higher admission LDH levels were associated with unfavorable outcomes (mRS 3-6; p=0.002) and were significantly elevated in total anterior circulation infarcts (total anterior circulation infarction: 354.1±165 U/L) compared to lacunar infarcts (lacunar infarction: 312.1±141 U/L; p=0.077). First-week LDH levels were significantly higher in cardioembolic strokes compared with large-artery atherosclerosis (cholesteryl ester: 302 U/L vs. LAA: 248 U/L; p=0.006). In ICH, higher first-week LDH levels were associated with unfavorable outcomes, particularly in deep hematomas. In multivariate analysis, chronic kidney disease (B=63.1, p=0.017), female sex (B=47.9, p=0.004), and unfavorable outcome (B=58.4, p=0.008) were independently associated with elevated admission LDH.

Conclusion: LDH levels alone do not distinguish between AIS and ICH, but higher admission values and sustained elevation are associated with poorer 3-month functional outcome, especially in ischemic stroke subtypes with larger infarcts or cardioembolic origin, and in deep ICH. LDH may be a marker that contributes to early risk stratification, yet the retrospective single-center design, small hemorrhagic subgroup, and exploratory multiple comparisons mean that these findings should be interpreted with caution and confirmed in prospective studies.

Keywords: Intracerebral hemorrhage, acute ischemic stroke, lactate dehydrogenase, prognosis, modified Rankin Scale

ÖZ

Amaç: Laktat dehidrogenaz (LDH), hücresel hasarın bir belirteci olup, inmede prognostik değeri giderek daha fazla kabul görmektedir. Bununla birlikte, farklı inme tiplerinin ayırt edilmesindeki ve klinik sonuçların öngörülmesindeki rolü henüz tam olarak açıklığa kavuşmamıştır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmada 2018-2023 yılları arasında takip edilen 1,299 hasta [1,185 akut iskemik inme (Aİİ), 114 intraserebral hemoraji (İSH)] analiz edildi. Başvuru sırasında ve ilk hafta ölçülen LDH düzeyleri inme tipleri, etiyolojileri ve klinik sonuçlar açısından karşılaştırıldı. Fonksiyonel durum, 3. ay modifiye Rankin Ölçeği (mRS) ile değerlendirildi. Başvuru LDH düzeyi ile bağımsız ilişkili faktörleri belirlemek amacıyla çok değişkenli aşamalı doğrusal regresyon analizi kullanıldı.

Bulgular: Ortalama başvuru LDH düzeyi Aİİ grubunda 329,3±176,1 U/L, İSH grubunda ise 342,4±174,9 U/L idi (p=0,45). İlk hafta LDH düzeyleri sırasıyla Aİİ grubunda 276,2±148,1 U/L ve İSH grubunda 300,1±123 U/L olarak bulundu (p=0,19). Aİİ grubunda, yüksek başvuru LDH düzeyleri

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kötü fonksiyonel sonuç (mRS 3-6) ile ilişkiliydi (p=0,002) ve total anterior sirkülasyon infarktı (total anterior dolaşım infarktı: 354,1±165 U/L) olan hastalarda laküner infarkt (laküner infarct: 312,1±141 U/L) olanlara kıyasla daha yüksek saptandı (p=0,077). İlk hafta LDH düzeyleri kardiyoembolik inmelerde büyük arter aterosklerozuna (LAA) bağlı inmelere göre anlamlı derecede daha yüksekti (302 U/L'ye karşı 248 U/L; p=0,006). İSH grubunda ise ilk hafta LDH düzeylerinin yüksek olması, özellikle derin yerleşimli hematomlarda olmak üzere kötü fonksiyonel sonuçlarla ilişkili bulundu. Çok değişkenli analizde kronik böbrek hastalığı (B=63,1, p=0,017), kadın cinsiyet (B=47,9, p=0,004) ve kötü fonksiyonel sonuç (B=58,4, p=0,008), yüksek başvuru LDH düzeyleri ile bağımsız olarak ilişkiliydi.

Sonuç: LDH düzeyleri tek başına Aİİ ile İSH'yi ayırt etmede yeterli değildir. Ancak yüksek başvuru LDH düzeyleri ve ilk haftada devam eden yüksek seyir, özellikle daha geniş infarkt alanına veya kardiyoembolik kökene sahip iskemik inme alt tiplerinde ve derin yerleşimli İSH olgularında, 3. ayda daha kötü fonksiyonel sonuçlarla ilişkilidir. LDH, erken risk sınıflandırmasına katkı sağlayabilecek bir belirteç olabilir. Bununla birlikte, çalışmanın retrospektif ve tek merkezli tasarımı, hemorajik alt grubun küçük olması ve çoklu karşılaştırmaların keşifsel nitelikte yapılmış olması nedeniyle bulgular dikkatle yorumlanmalı ve ileriye dönük çalışmalarla doğrulanmalıdır.

Anahtar Kelimeler: İntraserebral kanama, akut iskemik inme, laktat dehidrogenaz, prognoz, modifiye Rankin ölçeği

INTRODUCTION

Stroke remains a leading cause of mortality and long-term disability worldwide[1]. Biomarkers that facilitate stroke subtype differentiation and prognostic stratification may improve clinical decision-making and patient outcomes. Lactate dehydrogenase (LDH) is a ubiquitous intracellular enzyme involved in glycolysis, catalyzing the conversion of pyruvate to lactate under anaerobic conditions[2,3]. It is released into the circulation following cellular membrane damage and has therefore been considered a potential biomarker of tissue injury. However, LDH is a non-specific marker and may be influenced by a wide range of systemic conditions, which should be taken into account when interpreting its clinical significance. Elevated LDH levels have been associated with poor outcomes in various clinical settings, including malignancies, cardiovascular diseases, sepsis, and hypoxic–ischemic events[4]. In recent years, interest in LDH as a prognostic biomarker in neurological disorders, particularly stroke, has increased[2,4].

In intracerebral hemorrhage (ICH), LDH has been associated with hematoma expansion and unfavorable outcomes, likely reflecting inflammatory processes and microvascular injury mechan isms[5]. Radiological markers, such as computed tomography (CT) angiography spot sign and non-contrast CT blend sign, can help predict hematoma growth; however, these findings may be subject to interobserver variability. In contrast, serum biomarkers such as LDH may provide a more objective and widely accessible approach for early risk stratification. Similarly, although evidence is more limited, LDH has also been associated with adverse outcomes in acute ischemic stroke (AIS)[2,4]. Inflammation, anaerobic metabolism, and cellular necrosis within the ischemic penumbra may contribute to elevated LDH levels in these patients.

Composite biomarkers, such as the LDH-to-albumin ratio (LAR), have emerged as indicators of systemic inflammation, nutritional status, and oxidative stress factors that may influence stroke outcomes[6]. Although an increasing number of studies have evaluated LDH or LAR in ischemic and hemorrhagic stroke, direct comparisons of LDH dynamics across both stroke types within a single cohort remain scarce. Previous studies have reported associations between higher LDH levels or LAR and adverse functional outcomes, mortality, early onset cognitive impairment, and post-stroke depression in both AIS and ICH[4-8].

This study aimed to investigate the association between serum LDH levels and stroke type, severity, localization, and short-term outcomes in patients with acute ischemic or hemorrhagic stroke. The primary objective was to evaluate whether admission and first week LDH levels are associated with third-month functional outcome, assessed by the modified Rankin Scale (mRS), in both AIS and ICH. Given the non-specific nature of LDH and the heterogeneity of stroke pathophysiology, we further aimed to determine whether LDH functions as a complementary biomarker reflecting tissue injury burden rather than a disease-specific diagnostic marker. Secondary exploratory objectives included evaluating the relationship between LDH levels and stroke localization (Bamford classification)[9], etiological subtypes (TOAST classification)[10], vascular risk factors, and laboratory parameters.

MATERIALS AND METHODS

This retrospective, observational study was conducted following approval by the Trakya University Non-Interventional Studies Ethical Committee (approval no: TÜTF-GOBAEK 2024/32, decision no: 13/12, date: 19.08.2024). Written informed consent for the use of clinical and laboratory data was obtained from all patients at the time of hospitalization. Due to the retrospective design, no additional informed consent was required. Previously recorded electronic and written data were analyzed. All procedures were performed in accordance with the Declaration of Helsinki and local ethical regulations.

Study Population

Patients with acute AIS or primary ICH who were hospitalized in the Neurology Service between January 2018 and December 2023 were consecutively enrolled. The diagnosis of AIS was confirmed according to World Health Organization criteria

and neuroimaging findings (brain CT or magnetic resonance imaging). ICH diagnosis was established by non-contrast CT performed within 24 hours of symptom onset.

Inclusion criteria were: age ≥18 years; symptom onset within 72 hours for AIS or within 24 hours for ICH; and availability of baseline clinical and laboratory data. Exclusion criteria included secondary causes of ICH (e.g., cerebral aneurysm, arteriovenous malformations, moyamoya disease, trauma, tumors, or hemorrhagic transformation of infarction), prior major surgery or infection within 90 days, history of malignancy, transient ischemic attacks, and treatment with intravenous thrombolysis or endovascular mechanical thrombectomy. Patients with recent major surgery, active infection, or known malignancy were excluded to minimize potential confounding effects on LDH levels. However, due to the retrospective design, other conditions that may influence LDH levels could not be systematically controlled. Patients requiring primary intensive care unit admission at stroke onset were not included in this neurology ward–based cohort, which should be considered when interpreting the ICH subgroup findings. The flow diagram of patient inclusion and exclusion is shown in Figure 1.

Data Collection and Methods

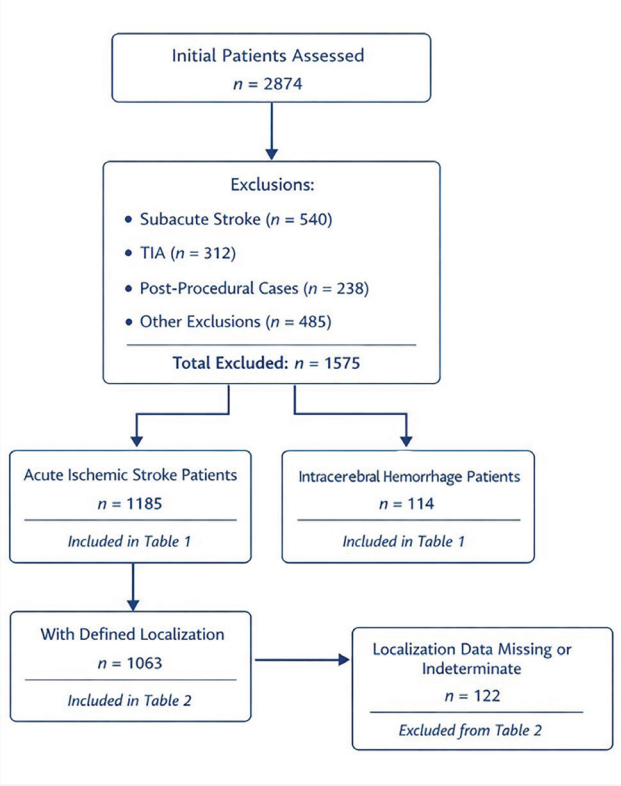

Figure 1. Flow diagram of patient selection and study inclusion

TIA: Transient ischemic attack

Comprehensive clinical data were extracted from inpatient electronic and written records by trained personnel. Demographic variables included age and sex (as recorded in official identity records). Medical history variables included hypertension (HT), diabetes mellitus (DM), dyslipidemia, heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD), prior stroke, smoking status, alcohol use, atrial fibrillation (AF), and use of antiplatelet or anticoagulant agents, in accordance with previous literature[4,6]. Length of stay (LOS) was defined as the number of hospitalization days.

After classification into ischemic and hemorrhagic stroke groups, further sub-classification was performed. Hemorrhagic stroke was categorized as lobar or deep, and anatomical localization (basal ganglia, thalamus, cerebellum, brainstem, lobar) was recorded. AIS was classified according to localization using the Bamford classification [total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI), lacunar infarction (LACI)] and according to etiology using the TOAST classification [cardioembolism (CE), large artery atherosclerosis (LAA), small vessel disease (SVD), unknown etiology (UE), and other determined etiology (OE)][9,10].

Stroke severity was assessed using the National Institutes of Health Stroke scale (NIHSS), and functional outcome was assessed using the third-month mRS[11,12]. NIHSS scores were obtained from hospitalization records, and mRS scores from third-month outpatient follow-up visits. An mRS score of 0-2 was defined as favorable outcome and ≥3 as unfavorable outcomes.

Laboratory parameters obtained from blood samples within 24 hours of admission included total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, urea, creatinine, LDH, white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), platelet count (PLT), mean corpuscular volume (MCV), hematocrit (HCT), neutrophil and lymphocyte percentages, neutrophil-to-lymphocyte ratio (NLR), and erythrocyte sedimentation rate. Follow-up LDH levels at one week were also recorded.

Demographic and laboratory variables were compared between ischemic and hemorrhagic stroke groups. In AIS, admission and first week LDH levels were analyzed according to localization, etiology, vascular risk factors, and outcomes. In ICH, LDH levels were evaluated according to localization, vascular risk factors, and outcome. The change in LDH between admission and the first week was categorized as an increase or decrease and analyzed in relation to outcomes. Correlations between admission LDH and clinical variables (stroke severity, NLR, LOS, and outcome) were assessed. A multivariable regression model was used to explore factors associated with admission LDH; in this model, admission LDH was treated as the dependent

variable, and clinical variables, including outcome measures, were included as independent variables to assess associations rather than imply causality.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies (percentages). Group comparisons were conducted using the χ^2 test or Fisher's exact test for categorical variables, and Student's t-test, one-way ANOVA, Mann-Whitney U test, or Kruskal-Wallis test for continuous variables, as appropriate. Pearson or Spearman correlation analyses were used depending on data distribution.

A multivariable stepwise linear regression model was used to explore factors associated with admission LDH. Variables included age, sex, AIS localization, AIS etiology, admission NIHSS, third-month mRS, NLR, HGB, urea, CKD, MCV, LOS, and anticoagulant use. Results are presented as unstandardized regression coefficients (B) with corresponding p-values. The multivariable model was constructed using a stepwise selection procedure; however, given the known limitations of stepwise methods, including potential instability and sensitivity to sample variation, the findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Given the number of subgroup and correlation analyses performed, no formal adjustment for multiple comparisons was applied, and these analyses should be interpreted cautiously. All analyses were performed under the supervision of a biostatistician. A two-sided p-value <0.05 was considered statistically significant for primary analyses.

RESULTS

A total of 2.874 stroke hospitalizations between January 2018 and December 2023 were screened. After excluding subacute strokes, transient ischemic attacks, and patients hospitalized for interventional or diagnostic procedures, 1.185 patients with AIS and 114 patients with ICH were included in the final analysis.

Baseline demographic and clinical characteristics are summarized in Table 1. Vascular risk factors, including HT, DM, dyslipidemia, smoking, AF, and HF, were more frequent in AIS than in ICH. LOS was longer in patients with ICH (p=0.002). No significant differences were observed in admission or first week LDH levels between AIS and ICH groups. No clinically useful LDH cut-off value was identified for differentiating between stroke types.

In AIS, admission LDH levels showed a non-significant trend across localization subtypes (p=0.077), with higher values observed in TACI compared with other subtypes. Female sex and CKD were associated with higher LDH levels across all localization groups. Higher admission LDH levels were also associated with unfavorable outcomes. Admission LDH levels according to localization and their associations with vascular risk factors are presented in Table 2. For localization-based analyses, only patients with clearly defined ischemic stroke subtypes according to the Bamford classification were included; patients with missing or indeterminate localization data were excluded, which accounts for the difference in sample size (1132 vs. 1185) compared to Table 1.

First week LDH levels differed across ischemic stroke localizations, with higher levels in TACI (p=0.016): TACI LDH 321 (130-950), PACI 270 (110-977), POCI 280 (114-1914), LACI 262 (22-1914). Higher first week LDH levels were observed in women in all AIS localization groups (TACI 331 vs. 312; PACI 288 vs. 255; POCI 311 vs. 257; LACI 271 vs. 257; p=0.004). Other risk factors for higher first week LDH were CKD in PACI (288 vs. 269), POCI (357 vs. 268), LACI (322 vs. 257) (p=0.014); anticoagulant use in POCI (433 vs. 270) (p=0.038); and AF in all groups (TACI 356 vs. 300; PACI 296 vs. 262; POCI 345 vs. 269; LACI 295 vs. 254; p<0.001). Higher first week LDH levels were associated with unfavorable outcome in PACI (264 vs. 254), POCI (474 vs. 248), and LACI (303 vs. 261) (p=0.015). Given the number of subgroup comparisons, these associations should be interpreted as exploratory.

There was no significant association between admission LDH levels and etiological classification of AIS [cardioembolic (CE) 340, LAA 337, SVD 335, UE 319, Other 244; p=0.14]. Females had higher LDH levels than males in all etiological groups (CE 354 vs. 325; LAA 344 vs. 354; SVD 337 vs. 334; UE 348 vs. 301; Other 339 vs. 262; p=0.005). CKD was associated with higher LDH in CE (351 vs. 339), LAA (367 vs. 336), and UE (400 vs. 310) etiological groups (p=0.004). Anticoagulant use in CE (356 vs. 336) and UE (484 vs. 309) was associated with higher LDH levels (p=0.001). Unfavorable outcome was associated with higher admission LDH in LAA (387 vs. 302) and UE (428 vs. 301) AIS groups (p=0.002).

First week LDH levels differed significantly according to AIS etiology (p=0.006): CE 302, LAA 248, SVD 257, UE 279, Other 237. Higher first week LDH levels were associated with female sex in CE (325 vs. 278), LAA (258 vs. 243), UE (298 vs. 268), and Other (249 vs. 213) (p=0.004); CKD in CE (355 vs. 297), SVD (471 vs. 238), and UE (303 vs. 277) (p=0.014); anticoagulant use in UE (376 vs. 274) (p=0.038); and AF in CE (316 vs. 276) and UE (319 vs. 276) (p<0.001). Higher first week LDH levels were associated with unfavorable outcome in CE (349 vs. 293) and UE (358 vs. 257) groups (p=0.015).

The distribution of admission and first week LDH among AIS types is shown in Figure 2. Overall, LDH levels decreased

Table 1. Demographic data between ischemic and hemorrhagic strokes

	Ischemic stroke n=1185	Hemorrhagic stroke n=114	p
Female	505 (42.6%)	48 (42.1%)	0.91
Age	68.64 (SD 13.3)	68.24 (SD 13)	0.75
Hypertension	801 (67.6%)	60 (52.6%)	0.002
Diabetes mellitus	481 (40.6%)	34 (29.8%)	0.032
Dyslipidemia	333 (28.1%)	18 (15.8%)	0.007
CAD	279 (23.5%)	21 (18.4%)	0.24
Stroke history	49 (4.1%)	5 (4.4%)	0.8
CKD	117 (9.9%)	12 (10.5%)	0.82
HF	112 (10.3%)	4 (3.5%)	0.019
Smoking	279 (23.5%)	16 (14%)	0.019
Alcohol	112 (9.5%)	8 (7%)	0.49
Anti-aggregant	372 (31.4%)	26 (22.8%)	0.07
Anti-coagulant	112 (10.3%)	10 (8.8%)	0.74
AF	283 (23.9%)	9 (7.9%)	<0.001
LOS	11.57 (SD 8.2)	14.22 (SD 8.5)	0.002
Admission NIHSS	4.3 (SD 4.3)	4.8 (SD 4)	0.48
24-hour NIHSS	3.6 (SD 4.1)	4.2 (SD 4.1)	0.43
7-day NIHSS	3.1 (SD 3.7)	3.7 (SD 3.9)	0.41
Third-month mRS	1.05 (SD 1.5)	1.88 (SD 2.3)	0.037
WBC	9.4 (SD 3.3)	9.9 (SD 3.7)	0.12
RBC	4.55 (SD 0.6)	4.58 (SD 0.5)	0.57
PLT	256.8 (SD 95)	249 (SD 83)	0.41
Hemoglobin	13.2 (SD 1.9)	13.1 (SD 1.8)	0.62
MCV	86.6 (SD 7.1)	86.2 (SD 5.58)	0.53
HCT	39.5 (SD 5.4)	39.2 (SD 5.1)	0.53
NLR	4.76 (SD 6.2)	5.67 (SD 5.5)	0.13
Urea	43.2 (SD 19.8)	39.9 (SD 19.8)	0.08
Creatinine	0.99 (SD 0.7)	0.94 (SD 0.5)	0.45
Admission LDH	329.3 (SD 176.1)	342.4 (SD 174.9)	0.45
First week LDH	276.2 (SD 148.1)	300.1 (SD 123)	0.19
Total-C	189.2 (SD 50.2)	184.6 (SD 46.8)	0.4
LDL-C	125.4 (SD 39.4)	119.8 (SD 35.7)	0.19
HDL-C	40.5 (SD 10.8)	43.8 (SD 12.3)	0.005
TG	148.2 (SD 94.2)	124 (SD 67.3)	0.019

Values are presented as mean ± standard deviation or n (%). Units: WBC and PLT ($\times 10^3/\mu L$), RBC ($\times 10^6/\mu L$), hemoglobin (g/dL), urea (mg/dL), creatinine (mg/dL), LDH (U/L), total cholesterol (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), triglycerides (mg/dL). CAD: Coronary artery disease, CKD: Chronic kidney disease, HF: Heart failure, AF: Atrial fibrillation, LOS: Length of stay in days, NIHSS: National Institutes of Health Stroke scale, mRS: modified Rankin Scale, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, MCV: Mean corpuscular volume, HCT: Hematocrit, LDH: Lactate dehydrogenase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, p-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and Student's t-test or ANOVA for continuous variables

by the first week in most AIS subtypes. The magnitude of change did not significantly differ by localization [TACI mean ± standard deviation (SD) LDH difference –35±202, PACI –77 ± 201, POCI –41±189, LACI –47±176; p=0.108], but differed across etiological subtypes (CE –33±204, LAA –103±231, SVD –69±146, UE –45±164, OE +6±113; p=0.003), with smaller reductions observed in cardioembolic stroke. An increase in LDH was associated with unfavorable outcome, particularly in TACI and POCI subtypes.

In hemorrhagic stroke, admission LDH levels did not differ significantly according to anatomical localization (basal

Table 2. Admission LDH levels according to AIS localization and vascular risk factors

		TACI n=130 LDH mean (SD)	PACI n=474 LDH mean (SD)	POCI n=226 LDH mean (SD)	LACI n=302 LDH mean (SD)	Total n=1132 LDH mean (SD)	p
Sex	Female	362 (153)	348 (174)	354 (313)	327 (165)	346 (199)	0.005
	Male	345 (171)	327 (177)	303 (120)	301 (139)	316 (155)	
HT	Yes	344 (151)	329 (149)	316 (127)	305 (142)	322 (143)	0.061
	No	379 (189)	354 (221)	332 (327)	323 (164)	343 (230)	
DM	Yes	344 (132)	329 (152)	304 (120)	317 (165)	323 (148)	0.33
	No	361 (182)	342 (190)	333 (256)	308 (139)	333 (193)	
Dyslipidemia	Yes	374 (163)	323 (130)	325 (134)	305 (132)	324 (136)	0.538
	No	347 (162)	342 (190)	319 (235)	314 (100)	331 (189)	
CAD	Yes	377 (162)	344 (237)	282 (100)	318 (155)	331 (190)	0.829
	No	345 (162)	335 (152)	330 (228)	309 (148)	328 (171)	
Prior stroke	Yes	449 (158)	326 (152)	330 (177)	284 (103)	328 (152)	0.985
	No	351 (162)	337 (177)	321 (212)	313 (151)	329 (177)	
HF	Yes	370 (150)	363 (156)	278 (114)	376 (208)	354 (165)	0.11
	No	151 (164)	333 (177)	325 (217)	305 (141)	326 (177)	
CKD	Yes	417 (190)	361 (152)	414 (482)	331 (169)	375 (284)	0.004
	No	347 (158)	334 (178)	307 (124)	310 (150)	324 (159)	
Alcohol	Yes	393 (230)	320 (185)	310 (154)	326 (130)	328 (169)	0.976
	No	350 (154)	338 (175)	322 (216)	310 (152)	329 (176)	
Smoking	Yes	341 (168)	358 (282)	301 (109)	301 (131)	326 (201)	0.731
	No	356 (161)	331 (134)	328 (234)	312 (150)	330 (167)	
Outcome	Favorable	326 (207)	314 (150)	314 (133)	302 (150)	310 (147)	0.002
	Unfavorable	385 (180)	353 (137)	515 (712)	250 (50)	379 (309)	
TOAST	CE	322 (143)	352 (285)	320 (129)	340 (172)	340 (169)	0.143
	LAA	368 (178)	355 (230)	318 (144)	290 (132)	337 (192)	
	SVD	-	328 (140)	317 (87)	348 (206)	335 (164)	
	Un-known	374 (164)	317 (127)	325 (274)	300 (125)	319 (174)	
	Other	-	278 (77)	243 (118)	224 (79)	244 (80)	

Values are presented as mean (standard deviation). LDH is expressed in U/L. TACI: Total anterior circulation infarction, PACI: Partial anterior circulation infarction, POCI: Posterior circulation infarction, LACI: Lacunar infarction, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease, HF: Heart failure, AIS: Acute ischemic stroke, CE: Cardioembolic, LAA: Large-artery atherosclerosis, SVD: Small-vessel disease, TACI: Total anterior circulation infarction, SD: Standard deviation, LDH: Lactate dehydrogenase, p-values were calculated using one-way ANOVA. Some subgroups show wide SD due to small sample sizes and outlier values. Given the number of subgroup comparisons, these analyses should be interpreted as exploratory

ganglia, thalamus, cerebellum, brainstem, or lobar) (p=0.18). Similarly, first week LDH levels were not significantly different across localization groups (p=0.094). When categorized as deep vs. lobar hemorrhage, LDH levels were comparable both at admission (344±190 vs. 339±107; p=0.89) and at first week (291±130 vs. 318±108; p=0.38).

Admission LDH levels were not associated with outcome in either deep or lobar hematomas (p=0.36). However, at first week, elevated LDH levels were significantly associated with unfavorable outcome in deep hematomas (560 vs. 290; p=0.014), largely driven by high LDH levels in basal ganglia hemorrhages. Smoking was associated with higher admission LDH in deep compared with lobar hematomas (619 vs. 250; p=0.004). No other consistent associations between vascular risk factors and LDH levels were observed in the ICH subgroup.

Analyses of LDH change between admission and first week showed that an increase in LDH was more frequently related to unfavorable outcome in hemorrhagic stroke than in AIS (p=0.012). An increase in LDH was more frequently associated with HT in ischemic strokes than in hemorrhagic ones (p=0.02). No other vascular risk factors were consistently related to LDH difference between AIS and ICH. In AIS, both etiologic and localization classifications showed predominantly decreased LDH at first week (68.8% decrease vs. 31.2% increase), with

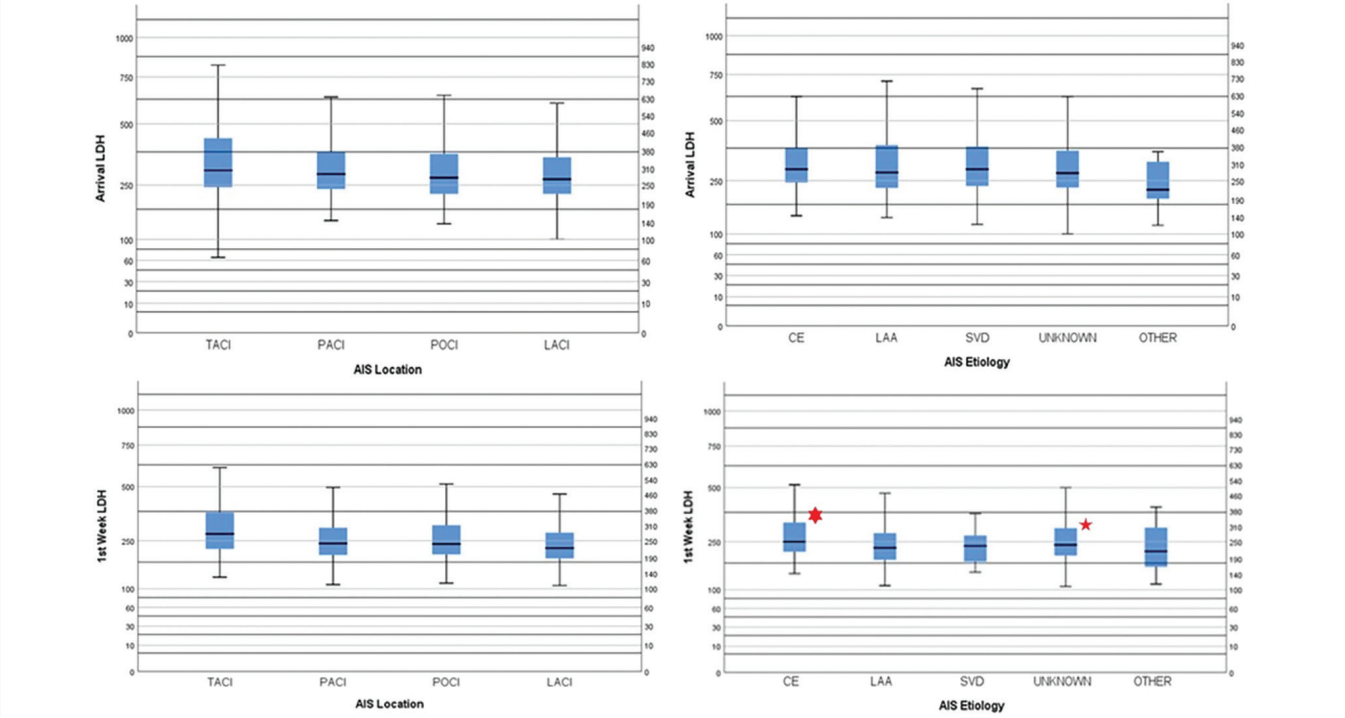

Figure 2. Admission and first week LDH levels among AIS types

*LDH was presented as U/L. Arrival LDH: admission LDH. Boxes represent interquartile ranges, horizontal lines indicate medians, and whiskers represent minimum and maximum values. *Persistent elevation of LDH at first week was observed particularly in TACI and in cardioembolic and undetermined etiology subgroups, AIS: Acute ischemic stroke, LDH: Lactate dehydrogenase, TACI: Total anterior circulation infarction, PACI: Partial anterior circulation infarction, POCI: Posterior circulation infarction, LACI: Lacunar infarction, CE: Cardioembolic, LAA: Large-artery atherosclerosis, SVD: Small-vessel disease*

a more pronounced but still non-significant difference for etiologic classification (p=0.059 vs. 0.095). CE and UE etiologies showed more LDH increases than LAA, SVD, and OE. TACI and POCI showed more LDH increases than PACI and LACI. CE and UE showed more LDH increases than LAA in the presence of smoking (p=0.04) and dyslipidemia (p=0.004). LDH increase was associated with unfavorable outcome particularly in TACI and POCI (p=0.003). In hemorrhagic strokes, female lobar hematomas more often showed LDH increases than deep hematomas (p=0.043). Although non-significant (p=0.071), female BG and thalamic hematomas also tended to show greater LDH increases than other localizations. No other risk factors were clearly associated with LDH difference in hemorrhagic strokes.

Correlation analyses were performed using Pearson correlation (r) for normally distributed variables and Spearman rank correlation (rho) for non-normally distributed or ordinal variables. Statistically significant but numerically weak associations were observed between LDH levels and several clinical and laboratory parameters. Admission LDH was associated at the p<0.05 level with admission NIHSS (r=0.061), first week NIHSS (r=0.077), third-month mRS (rho=0.110), HGB (rho=0.071), RBC (rho=0.072), AIS etiology (rho = 0.076), CKD (rho=–0.065), and AF (rho=–0.060), and at the p<0.01 level with WBC (r=0.097), MCV (r=0.096), NLR (r=0.092), urea (r=0.092), LOS (r=0.110), outcome (rho=0.121), sex (rho=0.090), AIS localization (rho=–0.119), and anticoagulant treatment (rho=–0.091). First week LDH was associated at the p<0.05 level with age (r=0.079), urea (r=0.081), MCV (r=0.076), alcohol consumption (rho=0.075), and anticoagulant use (rho=–0.073), and at the p<0.01 level with admission NIHSS (r=0.113), first week NIHSS (r=0.118), third-month mRS (rho=0.163), WBC (r=0.128), NLR (r=0.183), LOS (r=0.112), AIS localization (rho=–0.136), AF (rho=–0.129), sex (rho=0.100), and outcome (rho=0.167). These correlation coefficients (absolute values generally ≤0.18) indicate small effect sizes despite statistical significance, reflecting the large sample size and underscoring that the clinical impact of these associations is modest.

In multivariable regression analysis, CKD, female sex, unfavorable outcome, and higher MCV were independently associated with higher admission LDH levels (Table 3). Among these, CKD and unfavorable outcome showed the strongest associations. Age demonstrated a borderline negative association (p=0.051). However, the overall explanatory value

Table 3. Multivariable linear regression analysis for admission LDH

Factor	B	p
Length of stay	0.040	0.385
Admission NIHSS	0.002	0.976
Third-month mRS	0.022	0.808
AIS localization	0.031	0.496
AIS etiology	0.016	0.718
Age	-0.088	0.051
NLR	0.048	0.280
Hemoglobin	0.038	0.439
Urea	0.021	0.691
Unfavorable outcome	58.401	0.008
CKD	63.071	0.017
Female	47.914	0.004
MCV	2.842	0.012

Values represent unstandardized regression coefficients (B) with corresponding p-values. The model was constructed using a stepwise selection procedure. The overall model fit was low (adjusted R^2=0.048), AIS: Acute ischemic stroke, NLR: Neutrophil-to-lymphocyte ratio, LDH: Lactate dehydrogenase, CKD: Chronic kidney disease, MCV: Mean corpuscular volume, NIHSS: National Institutes of Health Stroke scale, mRS: modified Rankin Scale

of the model was limited (adjusted R^2=0.048), indicating that LDH levels are influenced by multiple interacting factors rather than a single dominant predictor. The model was constructed using a stepwise selection procedure given the exploratory nature of the analysis.

DISCUSSION

In this large, single-center retrospective cohort, we evaluated the relationship between serum LDH dynamics and clinical characteristics in patients with AIS and ICH. Although mean LDH levels were slightly higher in hemorrhagic strokes, LDH alone was not sufficient to reliably differentiate between ischemic and hemorrhagic stroke. In ischemic stroke, LDH levels appeared to be related to lesion volume as inferred from localization, with higher levels in TACI compared with PACI and POCI. In both ischemic and hemorrhagic stroke, female patients and those with CKD had higher LDH levels. Elevated admission LDH was modestly associated with unfavorable outcome in AIS, particularly in LAA. In cardioembolic strokes, higher first week LDH, rather than admission levels, was associated with AF and unfavorable outcome. In ICH, higher first week LDH was associated with unfavorable outcome in deep hematomas. Multivariable regression indicated that CKD, higher MCV, female sex, and unfavorable outcome were independently associated with admission LDH. However, the overall explanatory value of the model was limited (adjusted R^2=0.048), indicating that these variables account for only a small proportion of LDH variability. Importantly, most correlations were numerically weak, reflecting small effect sizes; therefore, these findings should be interpreted as modest associations rather than strong predictors. These results support the view that LDH reflects a global injury response rather than a disease-specific or high-precision prognostic marker.

To our knowledge, no studies have simultaneously compared LDH across both ischemic and hemorrhagic stroke within a single cohort. Prior work has linked LDH to hematoma expansion and prognosis in ICH and to etiology, prognosis, and response to revascularization therapy in AIS[2,4-6,13]. In our study, admission LDH tended to be higher in hemorrhagic than ischemic stroke; however, substantial overlap and wide distributions in both groups precluded identification of a clinically reliable cut-off. Therefore, LDH alone cannot be used to distinguish stroke type in the absence of imaging, further emphasizing its non-specific nature as a biomarker. Current stroke guidelines recommend different management strategies in acute stroke, including different blood pressure targets for ischemic and hemorrhagic stroke[14,15]. Serum LDH levels may provide supportive information regarding the extent of tissue injury; however, LDH should not be considered a substitute for neuroimaging or a determinant of acute management decisions. In resource-limited settings, markedly elevated LDH may reflect more severe brain injury; however, its clinical utility remains supportive rather than directive. Future studies may further explore whether LDH can complement imaging and clinical parameters in assessing overall injury burden.

In line with the concept that LDH reflects cellular damage, we excluded ischemic stroke patients treated with thrombolysis or thrombectomy, as these procedures may cause additional cellular breakdown and influence LDH levels while also modifying outcomes through reperfusion of the ischemic penumbra. By focusing on patients who did not receive reperfusion therapy, we aimed to better characterize the independent association between LDH and outcome in AIS. Previous studies have reported that elevated pre-thrombolysis LDH is associated with poor third-month outcomes and a higher risk of symptomatic ICH in patients treated with rt-PA, while other studies have demonstrated associations between LDH or LAR and mortality, poor functional outcome, post-stroke depression, or early cognitive impairment even in non-reperfused AIS cohorts[6,7,13,16,17]. Our findings support a similar association between LDH and outcome in patients who did not receive thrombolysis. Because LDH is related to the extent of tissue injury, additional damage such as hemorrhagic transformation may increase LDH levels and worsen prognosis. Although hemorrhagic transformation was not specifically evaluated in this study, higher first week LDH showed a stronger association with third-month mRS than admission LDH, suggesting that persistent or increasing LDH may reflect ongoing tissue injury. However, given the retrospective design, this interpretation should be considered exploratory.

Most prior studies examining LDH and prognosis in ischemic stroke have used the TOAST classification. Consistent with our findings, higher admission LDH has been associated with poorer outcomes in LAA and in broader AIS or TIA cohorts[2,4,13,16,17]. These studies often included a higher proportion of male patients, and sex-specific differences in LDH were not explored. In our cohort, LDH levels were significantly higher in women with both AIS and ICH. This may reflect hormonal, genetic, or behavioral factors; however, the underlying mechanisms remain unclear, and causality cannot be inferred from this observational study. Further studies evaluating sex-specific determinants of LDH, including estrogen levels and LDH isoenzyme patterns, are warranted. As expected, higher LDH levels were also observed in patients with CKD, consistent with previous studies, and LDH correlated with urea levels[4]. Impaired clearance of nephrotoxic or inflammatory molecules may contribute to increased tissue injury and LDH release in this context. Associations between LDH and hematologic parameters (MCV, HCT, HGB) and inflammatory markers (NLR) may similarly reflect the interplay among inflammatory burden, nutritional status, and comorbid conditions. These findings should be considered hypothesis-generating and require confirmation in targeted studies.

Given the half-life of LDH, a decline in serum levels would be expected if cellular breakdown ceases. We observed that persistently elevated LDH beyond the first week was associated with cardioembolic stroke, particularly in patients with AF, and with anticoagulant use. One possible explanation is ongoing thrombus-related processes; however, we did not systematically assess intracardiac thrombi or anticoagulation adequacy, and the observed correlations were modest. Therefore, this interpretation should be considered exploratory and interpreted with caution. In cryptogenic stroke, persistent LDH elevation at first week may support further evaluation for cardioembolic sources, such as prolonged cardiac monitoring for paroxysmal AF. Our finding of higher LDH levels in TACI and in patients with higher NIHSS scores is consistent with previous reports linking LDH to lesion volume and stroke severity, supporting the concept that LDH reflects the overall burden of tissue injury[13].

When outcome was assessed using the third-month mRS, higher admission LDH levels were associated with scores of 3-6, indicating an unfavorable prognosis. Consistent with previous studies, our findings support an association between elevated LDH and poorer clinical outcomes in ischemic stroke, particularly in LAA at admission and in cardioembolic stroke at first week[2,4,13,16,17]. We also observed that increases in LDH from admission to the first week were associated with unfavorable outcomes, with a more pronounced relationship in hemorrhagic stroke than in AIS. However, because LDH change was analyzed dichotomously (increase vs. decrease), the magnitude of change could not be assessed, which may have reduced the sensitivity of this analysis. Clinically, an unexpected rise or failure of LDH to decline during the first week after stroke onset may reflect ongoing tissue injury and a higher risk of poor outcome. However, given the retrospective design, small ICH sample size, and lack of adjustment for multiple comparisons, LDH dynamics should be considered supportive rather than a stand-alone prognostic tool. LDH levels were also associated with LOS, although this relationship was modest. Beyond mortality and disability, previous studies have linked elevated LDH to post-stroke depression and early cognitive decline after AIS, suggesting that LDH may reflect broader aspects of brain injury and systemic response[7,18].

For hemorrhagic stroke, we observed that elevated LDH levels were associated with longer LOS and, in line with previous studies, with unfavorable prognosis at third-month mRS. Prior reports have demonstrated associations between admission LDH and hematoma volume as well as short-term mortality, and have identified LDH ≥220 U/L as a predictor of early hematoma expansion and poor outcome in ICH[5,19,20]. In our study, LDH levels tended to be higher in deep hematomas than in lobar ones, consistent with previous reports, although we did not observe statistically significant differences according to localization[19]. Elevated first week LDH was more strongly associated with poor outcome in deep hematomas. The lack of statistical significance in some comparisons may reflect the relatively small number of ICH cases and the exclusion of patients requiring intensive care, and should therefore be interpreted cautiously given the limited statistical power. We were also unable to define a robust prognostic cut-off for LDH, reinforcing its limited clinical applicability as a stand-alone marker. Similar to previous studies, our ICH cohort was restricted to spontaneous ICH; however, elevated LDH has also been associated with adverse outcomes and mortality in aneurysmal subarachnoid hemorrhage[5,19,20]. Additional studies have shown that LDH predicts early hematoma expansion and poor outcome in ICH and is associated with poor neurological outcome and mortality after aneurysmal subarachnoid hemorrhage, further supporting its role as a marker of brain injury severity[5,21-23].

Our multiple regression analysis showed that CKD, female sex, unfavorable outcome, and higher MCV were independently associated with admission LDH in acute stroke patients. Although statistically significant, the coefficients indicate modest associations and a limited explanatory contribution of the model. Given that the model was constructed using a stepwise selection procedure, which is known to be sensitive to sample variability and may yield unstable variable selection, these findings should be interpreted with caution and considered hypothesis-generating rather than confirmatory. Future studies examining LDH as an outcome biomarker should adjust for renal function and sex and consider hematologic

parameters to more accurately evaluate LDH's independent contribution.

Study Limitations

This study has several limitations. First, it is a retrospective, single-center analysis, which may limit generalizability and introduce residual confounding despite multivariable adjustment. Second, the hemorrhagic stroke subgroup (n=114) was relatively small, providing limited power for detailed localization and subgroup analyses. Third, our cohort includes only patients admitted to the neurology ward; those with very severe strokes requiring primary intensive care admission were not captured, particularly in the ICH group, likely biasing the sample toward less severe hemorrhages. Fourth, we performed multiple subgroup and correlation analyses without formal adjustment for multiple testing; therefore, p-values from these exploratory analyses should be interpreted cautiously, and statistically significant findings with small effect sizes should not be viewed as definitive. In addition, the multivariable model was constructed using a stepwise selection procedure, which may be sensitive to sample variability and yield unstable variable selection. Fifth, LDH change was analyzed dichotomously (increase vs. decrease), which limited the ability to assess the magnitude of change and may have reduced analytical sensitivity. Finally, we did not systematically assess all conditions that may elevate LDH levels, such as medications, comorbid diseases, hemorrhagic transformation of AIS, intracardiac thrombus burden, or detailed measures of anticoagulation, which could have provided additional mechanistic insight.

Among the strengths of our study are the large AIS sample (>1,000 patients), uniform laboratory measurements from a single center, and evaluation of both admission and first week LDH, allowing us to characterize dynamic changes rather than relying on a single time point. The inclusion of both ischemic and hemorrhagic strokes within the same cohort provides a broader perspective on LDH in acute cerebrovascular disease and confirms, in a real-world setting, the modest but consistent association between higher LDH and poorer outcomes.

CONCLUSION

In conclusion, LDH levels alone cannot differentiate between ischemic and hemorrhagic stroke. Elevated admission LDH is associated with poorer prognosis in both AIS and ICH, and persistent elevation during the first week is particularly linked to cardioembolic ischemic stroke and unfavorable outcomes in deep ICH. Given the modest effect sizes, retrospective design, and exploratory nature of the analyses, LDH should be considered a complementary biomarker reflecting overall tissue injury rather than a stand-alone diagnostic or prognostic tool. Future prospective, multicenter studies with predefined statistical approaches are needed to validate the prognostic role of LDH dynamics and to determine whether integrating LDH with established clinical and imaging parameters can improve risk stratification in acute stroke.

Ethics

Ethics Committee Approval: This retrospective, observational study was conducted following approval by the Trakya University Non-Interventional Studies Ethical Committee (approval no: TÜTF-GOBAEK 2024/32, decision no: 13/12, date: 19.08.2024).

Informed Consent: Due to the retrospective design, no additional informed consent was required. Previously recorded electronic and written data were analyzed.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., S.Ko, Design: S.K., S.Ko, Data Collection or Processing: S.K., S.Ko, Analysis or Interpretation: S.K., S.Ko, Literature Search: S.K., S.Ko, Writing: S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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