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Research Article

The relationship between serum ischemia-modified albumin levels and prognosis in acute ischemic stroke

Akut iskemik inmede serum iskemiye modifiye albümin düzeyleri ile prognoz arasındaki ilişki

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Abstract

Aim: This study aimed to investigate the association between serum ischemia-modified albumin (IMA) levels, stroke severity, and functional outcomes in adult patients diagnosed with acute ischemic stroke (AIS) in the emergency department.

Material and Methods: In this prospective observational study, 40 AIS patients and 20 age- and sex-matched healthy controls were enrolled. Serum IMA levels were measured at admission using a commercial ELISA kit. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS), and functional outcomes at 3 months were determined using the modified Rankin Scale (mRS), with scores ≥2 defined as poor functional outcome (PFO).

Results: Median IMA levels were significantly higher in AIS patients than controls. Elevated IMA was independently associated with AIS (adjusted OR: 1.18, 95% CI: 1.03–1.35, p = 0.015), severe stroke (adjusted OR: 1.38, 95% CI: 1.06–1.83, p = 0.018), and PFO at 3 months (adjusted OR: 1.16, 95% CI: 1.04–1.30, p = 0.008). ROC analysis identified IMA cutoffs of >58 ng/mL for AIS (AUC: 0.859), >76.7 ng/mL for severe stroke (AUC: 0.890), and >65.4 ng/mL for PFO (AUC: 0.854).

Conclusion: Serum IMA levels are elevated in AIS and correlate with both initial stroke severity and short-term functional outcomes. IMA may serve as a rapid, cost-effective biomarker for early risk stratification in AIS.

Keywords: acute ischemic stroke, ischemia-modified albumin, oxidative stress, prognosis, modified Rankin Scale, NIHSS, biomarker

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Öz

Amaç: Bu çalışmada, acil serviste akut iskemik inme (AİS) tanısı alan erişkin hastalarda serum iskemiye modifiye albümin (İMA) düzeyleri ile inme şiddeti ve fonksiyonel sonuçlar arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: Prospektif gözlemsel tasarımla yürütülen çalışmaya, 40 AİS hastası ve yaş-cinsiyet açısından eşleştirilmiş 20 sağlıklı kontrol alındı. Serum İMA düzeyleri başvuru anında ticari ELISA kiti ile ölçüldü. İnme şiddeti Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) ile değerlendirildi. Üçüncü ay fonksiyonel sonuçları, modifiye Rankin Skalası (mRS) ile belirlendi ve mRS ≥2 kötü fonksiyonel sonuç (KFS) olarak tanımlandı.

Bulgular: Medyan İMA düzeyleri AİS grubunda kontrol grubuna göre anlamlı derecede yüksekti. Yüksek İMA düzeyleri, AİS (düzeltilmiş OR: 1,18; %95 GA: 1,03–1,35; p = 0,015), şiddetli inme (düzeltilmiş OR: 1,38; %95 GA: 1,06–1,83; p = 0,018) ve 3. ayda KFS (düzeltilmiş OR: 1,16; %95 GA: 1,04–1,30; p = 0,008) ile bağımsız olarak ilişkiliydi. ROC analizi, AİS için >58 ng/mL (EAA: 0,859), şiddetli inme için >76,7 ng/mL (EAA: 0,890) ve KFS için >65,4 ng/mL (EAA: 0,854) eşik değerlerini belirledi.

Sonuçlar: Serum İMA düzeyleri, AİS hastalarında artmakta ve hem başlangıç inme şiddeti hem de uzun dönem fonksiyonel sonuçlarla ilişkili bulunmaktadır. İMA, AİS'te erken risk sınıflaması için hızlı ve düşük maliyetli bir biyobelirteç olarak kullanılma potansiyeline sahiptir.

Anahtar Kelimeler: akut iskemik inme, iskemiye modifiye albümin, oksidatif stres, prognoz, modifiye Rankin Skalası, NIHSS, biyobelirteç.

Introduction

Ischemic stroke occurs when a cerebral artery is occluded, leading to an immediate loss of blood flow and oxygen to a region of the brain [1]. It accounts for the majority of all stroke cases, and stroke remains one of the leading causes of death and long-term disability worldwide [2]. The sudden energy deprivation in brain tissue triggers a complex cascade of pathophysiological events – including loss of ATP, ion imbalance, excitotoxicity, inflammation, and oxidative injury – that result in neuronal cell death and irreversible neurological deficits [3, 4]. The extent of this ischemic brain injury, along with the timeliness of reperfusion therapy, largely determines clinical outcomes, making early prognostication crucial in acute ischemic stroke (AIS) management.

Oxidative stress is recognized as a key contributor to secondary brain injury in AIS. Excessive production of reactive oxygen species (ROS) during and after ischemia oxidizes lipids, proteins, and nucleic acids, exacerbating tissue damage [5]. The brain is especially vulnerable to ROS-mediated injury due to its high lipid content, high oxygen consumption, and relatively low antioxidant defenses [6]. Clinical studies have observed that patients with AIS exhibit elevated levels of oxidative stress biomarkers (e.g. malondialdehyde, F2-isoprostanes, oxidized DNA products), and higher levels of these molecules are associated with more severe strokes and worse functional outcomes [7, 8].

One specific blood biomarker of oxidative injury that has drawn attention is ischemia-modified albumin (IMA) [9]. IMA is generated when circulating albumin undergoes an N-terminal structural modification under ischemic and oxidative conditions, resulting in an altered albumin with a reduced capacity to bind transition metals like cobalt [10, 11]. Serum IMA levels have been shown to rise within the first 24 hours of an AIS and then gradually decline over the subsequent days [12]. This rapid increase suggests that IMA might serve as a real-time indicator of ischemic oxidative injury in the brain. Moreover, emerging evidence indicates that higher IMA levels are associated with more severe strokes – for example, IMA concentrations have shown positive correlations with infarct size (lesion volume on imaging) and with neurologic deficit severity as measured by the NIH Stroke Scale [13]. Such findings raise the possibility that IMA not only signals the presence of ischemia but might also reflect the extent of cerebral damage, and thereby the potential prognosis.

Despite these observations, the prognostic utility of IMA in AIS remains incompletely defined. Therefore, the aim of this study was to investigate the relationship between serum IMA levels and disease severity and outcomes in patients diagnosed with AIS in the emergency service.

Material and Methods

This propective observational study was carried out between May 18, 2023, and May 18, 2024, at the Emergency Medicine Department of Bursa Uludağ University Faculty of Medicine Hospital. The study was approved by the Bursa Uludağ University Clinical Research Ethics Committee (Date: 16.05.2023, Approval No: 2023-11/21) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). Written informed consent was obtained from every participant or an authorized surrogate.

The study involved 40 patients diagnosed with acute ischemic stroke and 20 age- and sex-matched healthy control subjects recruited during the same period from outpatient settings. Patients were included if they presented to the emergency department within the first 24 hours following symptom onset characterized by focal neurological deficits and received a definitive AIS diagnosis confirmed through neurological examination and neuroimaging modalities, including computed tomography (CT) or computed tomography angiography (CTA). Further inclusion criteria encompassed inpatient neurology clinic follow-up, complete diagnostic evaluation to elucidate stroke etiology, and a planned follow-up schedule at the neurology stroke clinic for three months after discharge to monitor clinical outcomes. Patients were excluded if baseline renal function was impaired (elevated serum urea or creatinine), if the required vascular imaging could not be completed, if the diagnostic evaluation for stroke etiology remained incomplete, if the patient was lost to follow-up, or if the patient had any acute condition that could affect serum IMA levels — including acute coronary syndrome, pulmonary embolism, or sepsis.

Study Protocol

All enrolled AIS patients underwent detailed clinical evaluations by neurologists or neurology residents at the time of admission to the emergency department. Diagnosis was confirmed based on clinical features consistent with AIS and supporting neuroimaging evidence. Patients' demographic details, including age and gender, along with medical histories (prior stroke, hypertension, coronary artery disease, diabetes mellitus, heart failure, atrial fibrillation, valvular heart diseases, and hepatic or renal impairment) and medication usage, were systematically documented from hospital records and discharge summaries. Stroke severity at admission was objectively quantified using the National Institutes of Health Stroke Scale (NIHSS).

Etiological Evaluation

To determine the underlying stroke etiology comprehensively, each patient underwent diagnostic investigations that included brain and neck CTA and/or cranial MRI, follow-up cranial CT scans, electrocardiography (ECG), and digital cerebral angiography as clinically indicated. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria by experienced neurologists. Radiological assessment of intracranial atherosclerosis was conducted by radiologists employing the North American Symptomatic Carotid Endarterectomy Trial (NASCET) methodology. Specifically, anterior circulation assessment encompassed the internal carotid artery (ICA) and its branches, whereas the posterior circulation assessment involved both vertebral arteries, the basilar artery, and associated branches.

Clinical Management and Follow-up

Patients received standardized stroke care according to contemporary guidelines, including appropriate pharmacological therapy and, when indicated, revascularization interventions. Follow-up was performed at three months after the initial event during outpatient appointments at the neurology stroke clinic, with particular attention given to stroke recurrence and clinical status. Clinical outcomes at follow-up were evaluated using the modified Rankin scale (mRS). Patients were categorized into two outcome groups based on the mRS score: good functional outcome (GFO; scores 0–1) and poor functional outcome (PFO; scores 2–6) [14, 15].

Measurement of Serum Ischemia-Modified Albumin

Peripheral venous blood samples were collected from all participants at the time of admission. Samples were promptly transferred to the Medical Biochemistry Laboratory, centrifuged at 20,000 rpm for 15 minutes, aliquoted into Eppendorf tubes, and stored at −80°C until biochemical analysis. Serum IMA levels were quantified using a commercially available Human Ischemia Modified Albumin enzyme-linked immunosorbent assay (ELISA) Kit (Bioassay Technology Laboratory, Cat No: E1172Hu), based on ELISA principles. All assays were performed according to manufacturer instructions in the Department of Medical Biochemistry with results expressed as ng/mL.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics, version 26.0. Continuous variables were tested for normality using Kolmogorov–Smirnov test. Normally distributed data are presented as mean ± standard deviation, and non-parametric data as median with interquartile range; categorical variables are given as frequencies and percentages. Group comparisons employed the independent-samples t-test or Mann–Whitney U test for continuous data and the χ^2 test or Fisher's exact test for categorical data. In addition to descriptive and comparative analyses, both crude and multivariable logistic regression models were constructed to assess the independent association between IMA levels and clinical outcomes. The adjusted models included age, sex, smoking status, comorbidities, and relevant laboratory parameters as covariates to account for potential confounding effects. ROC curve analysis was performed to determine the diagnostic performance (sensitivity, specificity, cut-off values) of IMA. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

A total of 40 AIS patients with a mean age of 65.9 ± 11.1 years and 20 healthy controls with a mean age of 63.3 ± 10.9 years were included in the study. The gender distribution and smoking rates were similar between the groups. Median IMA levels higher in AIS group compared to control group (Table 1).

Hypertension (92.5%) and diabetes mellitus (67.5%) were the most prevalent comorbidities among patients with AIS, followed by coronary artery disease (35%) and heart failure (20%). Cervicocerebral atherosclerotic stenosis was identified in 52.5% of the patients. The median leukoaraiosis score was 2. AIS patients had a median baseline NIHSS score of 7. Stroke severity was mild in 17.5%, mild to moderately severe in 57.5%, and severe in 25% of the patients. Median baseline NIHSS score of 7. Furthermore, patients had a median baseline mRS score of 3. Three months after stroke onset, patients had a median NIHSS score of 2.5 and a median mRS score of 2. Additionally, PFO was identified in 55% of the patients.

Patients with severe stroke had higher mean age (73.2 ± 10.6 vs. 62.4 ± 10.4, p = 0.014), median IMA levels (81.2 vs. 58.3, p < 0.001) (Figure 1), and baseline mRS scores (4 vs. 3, p = 0.007) compared to those without non-severe stroke. Moreover, all of these patients exhibited PFO at 3 months (Table 2).

Patients with PFO had higher diabetes mellitus (81.8 vs. 50.0, p = 0.046), median IMA levels (75.0 vs. 56.4, p < 0.001) (Figure 1), and baseline NIHSS scores (8 vs. 5, p < 0.001) compared to those with GFO (Table 3).

Higher IMA levels significantly increased the likelihood of AIS, with an odds ratio (OR) of 1.19 (95% CI: 1.07–1.32, p < 0.001) in the unadjusted model and 1.18 (95% CI: 1.03–1.35, p = 0.015) after adjustment for potential confounders. Likewise, elevated IMA levels were predictive of severe stroke compared to non-severe cases (crude OR: 1.19, 95% CI: 1.05–1.34, p < 0.001; adjusted OR: 1.38, 95% CI: 1.06–1.83, p = 0.018). Furthermore, higher IMA was independently associated with poor PFO at 3 months (adjusted OR: 1.16, 95% CI: 1.04–1.30, p = 0.008) (Table 4).

ROC analysis identified an IMA cutoff value of >58 for predicting AIS, with 75% sensitivity and 94.7% specificity (AUC ± SE = 0.859 ± 0.05). For the prediction of severe stroke, the cutoff value was >76.7 (90% sensitivity, 76.7% specificity; AUC = 0.890 ± 0.05). In predicting the PFO, a cutoff value of >65.4 yielded 87.4% sensitivity and 83.3% specificity (AUC = 0.854 ± 0.06) (Figure 2).

Table 1. Distribution of IMA levels in acute ischemic stroke group compared to an age- and sex-matched control group.

Variables	Control	AIS	p
	n = 20	n = 40	
Age, years	63.3 ± 10.9	65.9 ± 11.1	0.393
Gender, n (%)			
Female	7 (36.8)	16 (40.0)	0.816
Male	12 (63.2)	24 (60.0)	
Smoking, n (%)	5 (26.3)	17 (42.5)	0.230
IMA, ng/mL	52.2 (46.7-54.9)	62.0 (56.2-71.7)	<0.001*

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR). Student's t-test or Mann–Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. *P-value <0.05 shows statistical significance. Abbreviations: AIS, acute ischemic stroke; IMA, ischemia-modified albumin.

Table 2. Findings associated with stroke severity.

Variables	Non-severe n = 30	Severe n = 10	p
Age, years	62.4 ± 10.4	73.2 ± 10.6	0.014*
Female gender, n (%)	10 (33.3)	6 (60.0)	0.264
Smoking, n (%)	13 (43.3)	4 (40.0)	0.999
Hypertension, n (%)	28 (93.3)	9 (90.0)	0.999
Diabetes mellitus, n (%)	18 (60.0)	9 (90.0)	0.172
Heart failure, n (%)	7 (23.3)	1 (10.0)	0.648
CAD, n (%)	11 (36.7)	3 (30.0)	0.999
CCAS, n (%)	16 (53.3)	5 (50.0)	0.999
Leukoaraiosis	3 (2-4)	2 (1-3)	0.140
IMA, ng/mL	58.3 (55.1-62.8)	81.2 (69.1-100.0)	<0.001*
Glucose, mg/dL	122.5 (106-186)	128 (100-197)	0.166
HbA1C, %	6.7 ± 1.2	6.5 ± 1.1	0.668
LDL, mg/dL	114 (90-145)	78.5 (63-105)	0.056
Triglycerides, mg/dL	135.5 (98-191)	119 (86-142)	0.347
Creatinine, mg/dL	0.8 ± 0.3	0.7 ± 0.3	0.676
NIHSS			
Baseline	5 (5-8)	16 (15-18)	<0.001*
3rd month	2 (1-3)	11 (5-27)	<0.001*
Mild	28 (93.3)	1 (10.0)	<0.001*
Mild to Moderate	2 (6.7)	5 (50.0)	
Severe	0	4 (40.0)	
mRS			
Baseline	3 (2-3)	4 (3-5)	0.007*
3rd month	1 (1-2)	2 (2-5)	<0.001*
GFO, n (%)	18 (60.0)	0	0.003*
PFO, n (%)	12 (40.0)	10 (100.0)	

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR). * Numerical variables are mean (SD) or median (IQR). Student's t-test or Mann–Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. * P-value <0.05 shows statistical significance. Abbreviations: AIS, acute ischemic stroke; CAD, coronary artery disease; CCAS, cervicocerebral atherosclerotic stenosis; GFO, good functional outcome; HbA1C, hemoglobin A1c; IMA, ischemia-modified albumin; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; PFO, poor functional outcome.

Table 3. Findings associated with poor functional outcome.

Variables	GFO n = 18	PFO n = 22	p
Age, years	67.3 ± 10.5	68.4 ± 11.8	0.763
Female gender, n (%)	4 (22.2)	12 (54.5)	0.054
Smoking, n (%)	6 (33.3)	11 (50.0)	0.348
Hypertension, n (%)	17 (94.4)	20 (90.9)	0.999
Diabetes mellitus, n (%)	9 (50.0)	18 (81.8)	0.046*
Heart failure, n (%)	6 (33.3)	2 (9.1)	0.131
CAD, n (%)	7 (38.9)	7 (31.8)	0.744
CCAS, n (%)	8 (44.4)	13 (59.1)	0.525
Leukoaraiosis	3 (2-4)	3 (2-4)	0.640
IMA, ng/mL	56.4 (54.0-60.6)	75.0 (68.4-88.0)	<0.001*
Glucose, mg/dL	112.5 (95-142)	142 (110-213)	0.106
HbA1C, %	6.2 ± 1.0	6.9 ± 1.3	0.071
LDL, mg/dL	114 (90-127)	97 (67-126)	0.209
Triglycerides, mg/dL	131.5 (98-190)	135.5 (89-173)	0.925
Creatinine, mg/dL	0.7 ± 0.2	0.8 ± 0.3	0.344
NIHSS			
Baseline	5 (3-5)	8 (8-16)	<0.001*
3rd month	1 (1-2)	4 (3-10)	<0.001*
Mild	18 (100.0)	11 (50.0)	<0.001*
Mild to Moderate	0	7 (31.8)	
Severe	0	4 (18.2)	
Baseline mRS	2 (2-3)	3 (2-5)	0.020*

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR). * Numerical variables are mean (SD) or median (IQR). Student's t-test or Mann–Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. *P-value <0.05 shows statistical significance. Abbreviations: AIS, acute ischemic stroke; CAD, coronary artery disease; CCAS, cervicocerebral atherosclerotic stenosis; GFO, good functional outcome; HbA1C, hemoglobin A1c; IMA, ischemia-modified albumin; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; PFO, poor functional outcome.

Table 4. The impact of ischemia-modified albumin on acute ischemic stroke, stroke severity, and clinical outcomes.

Variables	OR (95% CI)	p
AIS (vs. control)		
Crude	1.19 (1.07-1.32)	<0.001
Adjusted	1.18 (1.03-1.35)	0.015
Severe stroke (vs. non-severe stroke)		
Crude	1.19 (1.05-1.34)	<0.001
Adjusted	1.38 (1.06-1.83)	0.018
PFO (vs. GFO)		
Crude	1.17 (1.05-.1.31)	<0.001
Adjusted	1.16 (1.04-1.30)	0.008

While crude regression analysis shows the direct (unadjusted) association of IMA with the outcome, the adjusted logistic regression model controls for confounding variables such as age, sex, smoking status, comorbidities, and relevant laboratory values to isolate the independent effect of IMA. Abbreviations: AIS, acute ischemic stroke; CI, confidence interval; GFO, good functional outcome; OR, odds ratio; PFO, poor functional outcome.

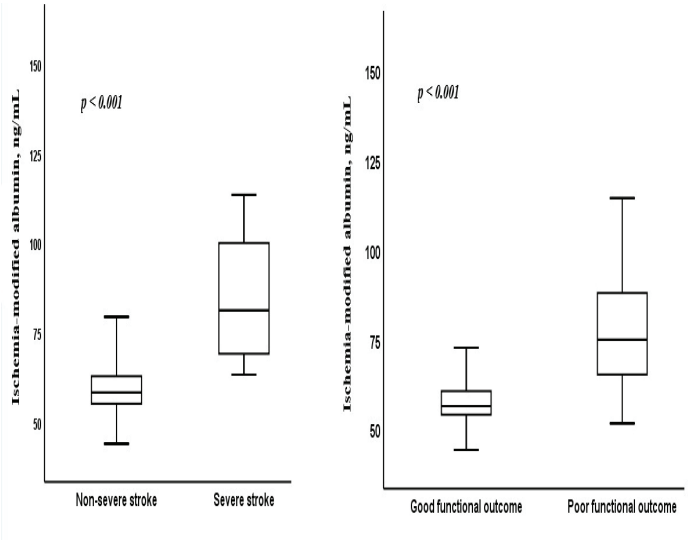

Figure 1. Distribution of ischemia-modified albumin in severe stroke and poor functional outcome.

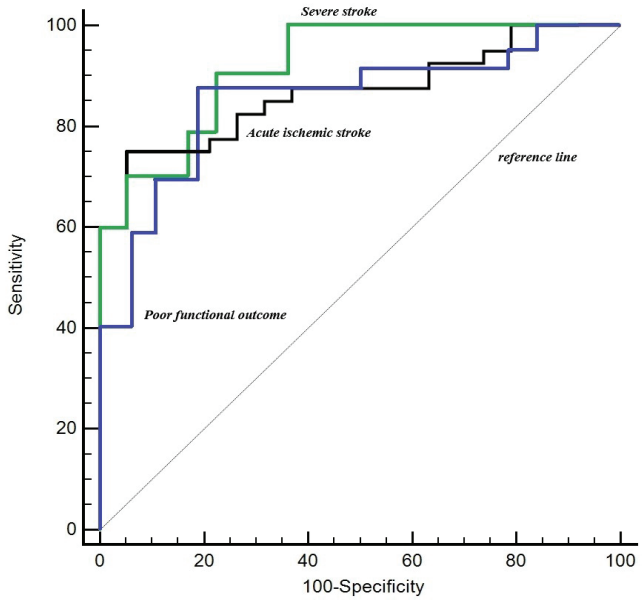

Figure 2. The diagnostic performance of IMA levels in predicting the presence of acute ischemic stroke, severe stroke, and poor functional outcome.

Discussion

Our study demonstrated that serum IMA levels were markedly elevated in patients with AIS compared to healthy controls and were significantly associated with both initial stroke severity and long-term functional outcomes. Higher IMA concentrations at admission independently predicted the presence of AIS, more severe neurological deficits, and poor functional outcome at three months, with strong diagnostic performance in ROC analyses. These findings suggest that IMA, a sensitive biomarker of ischemia and oxidative stress, may have clinical value in AIS—serving not only as an early diagnostic indicator but also as a prognostic tool for stratifying patients according to the risk of severe stroke and unfavorable recovery.

Multiple international studies have demonstrated that IMA levels are significantly elevated in patients with acute ischemic stroke compared to healthy controls [16, 17]. Menon et al. reported that serum IMA within the first hour of AIS was significantly higher than in healthy controls [18]. Arecent case–control study by Soliman et al. found mean IMA levels in acute stroke patients to be roughly double those of a control group [19]. Moreover, IMA tends to peak in the early acute phase of stroke and then gradually declines over the ensuing days [18]. Importantly, IMA appears elevated across different stroke subtypes – both ischemic and hemorrhagic – although levels tend to be higher in ischemic infarcts than intracerebral hemorrhages [19]. In a Turkish cohort, mean IMA in brain infarction was 0.280 ± 0.045 absorbance units versus 0.172 ± 0.045 in controls, underscoring that IMA rises significantly during acute cerebrovascular events [20]. Notably, that study also reported an area under the ROC curve of ~0.845 for IMA in distinguishing stroke patients from controls [20], consistent with the excellent diagnostic accuracy (AUC ~0.86) observed in our cohort. Previous studies have demonstrated that the sensitivity of IMA in predicting AIS ranges from 85% to 90% [18, 20-22]. The current results align well with those reported in the existing literature. These converging findings from diverse populations confirm that IMA is a robust biomarker of ischemic stroke presence.

Importantly, our study suggests that IMA is not only a diagnostic marker but also correlates with stroke severity and clinical prognosis. In one study, serum IMA demonstrated a significant correlation with NIHSS score and with infarct volume, indicating that larger ischemic injuries produce greater IMA release [23]. Another study found a significant correlation between IMA levels and the volume of diffusion-restricted tissue on MRI in acute stroke [24]. In the same study, IMA also showed a trend in parallel with NIHSS, as larger infarcts were associated with higher IMA [24]. Another study reported elevated IMA levels in patients with severe stroke and demonstrated a positive correlation between MRI-measured ischemic volume and IMA levels [25]. However, some studies have reported no association between IMA and the progression of AIS [19, 26]. We also found that elevated IMA predicted PFO, after adjusting for confounders. This aligns with preliminary observations by Nayak et al. that

persistently higher IMA levels in the days following stroke were associated with worse neurological status and outcomes [27]. Nevertheless, the prognostic utility of IMA in AIS remains an evolving area. Not all studies have observed a clear link between admission IMA and long-term outcomes. An Egyptian cohort found that baseline IMA did not significantly correlate with 3-month disability, whereas another biomarker (fibulin-5) did [24]. Such discrepancies suggest that while IMA shows promise as a prognostic indicator, its predictive power may depend on patient populations or be influenced by additional factors, underscoring the need for further large-scale studies.

The rise in IMA during acute stroke can be explained by the underlying pathophysiology of ischemia-reperfusion injury and oxidative stress. Albumin undergoes structural modifications under ischemic conditions that generate a pro-oxidative and acidic environment [28, 29]. In the presence of ROS and acidosis, the N-terminus of the albumin molecule is altered, reducing its capacity to bind transition metals – the biochemical change measured as "ischemia-modified" albumin [16]. Notably, the increase in IMA is transient. In stroke patients, IMA likewise peaks in the acute phase and declines over the next several days [18]. This transient surge reflects the acute burst of oxidative stress accompanying ischemic brain injury. In support of this, there is a strong positive correlation between IMA and direct oxidative stress markers in AIS patients. Jena et al. observed a highly significant correlation between serum IMA and malondialdehyde (MDA, a lipid peroxidation marker) levels in stroke [30]. They also noted that patients with AIS had increased IMA alongside decreased antioxidants (e.g. lower albumin and uric acid), reinforcing that oxidative stress plays a major role in the pathogenesis and severity of stroke [30]. Indeed, growing evidence implicates oxidative injury as a key contributor to ischemic stroke damage, which likely explains why IMA – essentially a footprint of oxidative albumin alteration – correlates with stroke severity and evolution [16]. In other words, higher IMA indicates a greater oxidative insult to tissues during the acute event, linking it to more extensive ischemic damage and potentially worse clinical outcomes.

Several limitations of our study should be acknowledged. First, this was a single-center study with a low sample size, which may limit the generalizability of the findings. Our cohort might not capture the full spectrum of stroke patients in other settings; larger multi-center studies are needed to validate the observed diagnostic cutoffs and risk estimates. Second, we measured IMA only upon admission and did not obtain serial IMA levels during hospitalization or recovery. Third, IMA is a nonspecific marker of ischemia. Elevated IMA has been documented in a variety of ischemic or oxidative stress conditions – including myocardial infarction, pulmonary embolism, critical limb ischemia, and even some systemic inflammatory states [20]. We attempted to control for major confounders, but it is possible that some patients had concurrent comorbidities contributing to IMA elevation. In addition, a longer follow-up beyond 3 months would also be informative to see if admission IMA predicts long-term outcomes (such as 1-year survival or dependency). Lastly, the observational nature of our study precludes any direct causal conclusions.

In conclusion, this study demonstrated that serum IMA levels were significantly elevated in patients with AIS compared to healthy controls, and that higher IMA concentrations at admission were independently associated with stroke severity and poor functional outcomes at three months. IMA showed strong diagnostic performance for identifying AIS and severe stroke, with clinically relevant cutoff values offering high sensitivity and specificity. These findings suggest that IMA, as a marker of oxidative stress and ischemic injury, may serve as a practical adjunct to established clinical and imaging assessments—providing both early diagnostic insight and prognostic stratification.

Ethical Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by Bursa Uludağ University Clinical Research Ethics Committee (Date: 16.05.2023, Decision No: 2023-11/21).

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Informed Consent

Written informed consent was obtained from every participant or an authorized surrogate.

Conflicts of Interest

Authors declare that they have no conflicts of interest.

Authors' Contribution

Concept – G.A. and A.D., Design- G.A. and A.D., Methodology – G.A., A.D., A.A.A., Y.D., B.A., and A.Y.O., Data collection and/or processing – G.A., A.D., A.A.A., Y.D., B.A., and A.Y.O., Analysis and/or interpretation – G.A., A.D., A.A.A., Y.D., B.A., and A.Y.O.,

Resources G.A., A.D., A.A.A., Y.D., B.A., and A.Y.O., Writing – G.A. Critical review- A.D., A.A.A., Y.D., B.A., and A.Y.O. All authors read and approved the final version of the manuscript

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References

1. Kuriakose D and Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. Int J Mol Sci. 2020;21(20) DOI: 10.3390/ijms21207609.
2. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization: Global Stroke Fact Sheet 2025. Int J Stroke. 2025;20(2):132-44. DOI: 10.1177/17474930241308142.
3. Qin C, Yang S, Chu YH, et al. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2022;7(1):215. DOI: 10.1038/s41392-022-01064-1.
4. Salaudeen MA, Bello N, Danraka RN, and Ammani ML. Understanding the Pathophysiology of Ischemic Stroke: The Basis of Current Therapies and Opportunity for New Ones. Biomolecules. 2024;14(3) DOI: 10.3390/biom14030305.
5. Kong J, Fan R, Zhang Y, et al. Oxidative stress in the brain-lung crosstalk: cellular and molecular perspectives. Front Aging Neurosci. 2024;16:1389454. DOI: 10.3389/fnagi.2024.1389454.
6. Elsayed WM, Abdel-Gawad E-HA, Mesallam DI, and El-Serafy TS. The relationship between oxidative stress and acute ischemic stroke severity and functional outcome. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2020;56(1):74.
7. Kamal FZ, Lefter R, Jaber H, Balmus IM, Ciobica A, and Iordache AC. The Role of Potential Oxidative Biomarkers in the Prognosis of Acute Ischemic Stroke and the Exploration of Antioxidants as Possible Preventive and Treatment Options. Int J Mol Sci. 2023;24(7) DOI: 10.3390/ijms24076389.
8. Maas MB and Furie KL. Molecular biomarkers in stroke diagnosis and prognosis. Biomark Med. 2009;3(4):363-83. DOI: 10.2217/bmm.09.30.
9. Coverdale JPC, Katundu KGH, Sobczak AIS, Arya S, Blindauer CA, and Stewart AJ. Ischemia-modified albumin: Crosstalk between fatty acid and cobalt binding. Prostaglandins Leukot Essent Fatty Acids. 2018;135:147-57. DOI: 10.1016/j.plefa.2018.07.014.
10. Bal W, Sokolowska M, Kurowska E, and Faller P. Binding of transition metal ions to albumin: sites, affinities and rates. Biochim Biophys Acta. 2013;1830(12):5444-55. DOI: 10.1016/j.bbagen.2013.06.018.
11. Watanabe H, Imafuku T, Otagiri M, and Maruyama T. Clinical Implications Associated With the Posttranslational Modification-Induced Functional Impairment of Albumin in Oxidative Stress-Related Diseases. J Pharm Sci. 2017;106(9):2195-203. DOI: 10.1016/j.xphs.2017.03.002.
12. Yeniocak S, Sarac F, Yazicioglu M, et al. The Diagnostic Values of Ischemia-Modified Albumin in Patients with Acute Abdominal Pain and Its Role in Differentiating Acute Abdomen. Emerg Med Int. 2020;2020:7925975. DOI: 10.1155/2020/7925975.
13. Shevtsova A, Gordiienko I, Tkachenko V, and Ushakova G. Ischemia-Modified Albumin: Origins and Clinical Implications. Dis Markers. 2021;2021:9945424. DOI: 10.1155/2021/9945424.
14. Chen T, Cui Y, and Chen HS. The association of gender with functional outcome in thrombolysed stroke: A secondary analysis of INTRECIS study. Heliyon. 2024;10(11):e32630. DOI: 10.1016/j.heliyon.2024.e32630.
15. Weisscher N, Vermeulen M, Roos YB, and de Haan RJ. What should be defined as good outcome in stroke trials; a modified Rankin score of 0-1 or 0-2? J Neurol. 2008;255(6):867-74. DOI: 10.1007/s00415-008-0796-8.
16. Mangoni AA and Zinellu A. A Systematic Review and Meta-Analysis of Serum Concentrations of Ischaemia-Modified Albumin in Acute Ischaemic Stroke, Intracerebral Haemorrhage, and Subarachnoid Haemorrhage. Biomolecules. 2022;12(5) DOI: 10.3390/biom12050653.
17. Shi W, Tang G, Zhou X, and Ye Y. Appraising the Accuracy of Ischaemia-Modified Albumin in Diagnosing Stroke: A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2021;50(4):365-70. DOI: 10.1159/000514382.
18. Menon B, Ramalingam K, and Krishna V. Study of Ischemia Modified Albumin as a Biomarker in Acute Ischaemic Stroke. Ann Neurosci. 2018;25(4):187-90. DOI: 10.1159/000488188.
19. Soliman HS, Okda MA, El-Kholy MS, and El-Kabany RA. Ischemia-modified albumin for evaluating severity and predicting prognosis in patients with acute cerebrovascular disease. Menoufia Medical Journal. 2020;33(3):1072-76.
20. Gunduz A, Turedi S, Mentese A, et al. Ischemia-modified albumin levels in cerebrovascular accidents. Am J Emerg Med. 2008;26(8):874-8. DOI: 10.1016/j.ajem.2007.11.023.

21. Ertekin B, Kocak S, Defne Dundar Z, et al. Diagnostic value of ischemia-modified albumin in acute coronary syndrome and acute ischemic stroke. Pak J Med Sci. 2013;29(4):1003-7.
22. Çakmak VA, Gündüz A, Karaca Y, Alioğlu Z, Menteşe A, and Topbaş M. Diagnostic Significance of Ischemia-Modified Albumin, S100b, and Neuron-Specific Enolase in Acute Ischemic Stroke. Journal of Academic Emergency Medicine/Akademik Acil Tip Olgu Sunumlari Dergisi. 2014;13(3).
23. Elshony HS, Okda MA, and El-Kabany RA. Ischemia-modified albumin and fibulin-5 as diagnostic and prognostic markers for acute cerebrovascular disease. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2021;57(1):12.
24. Can S, Akdur O, Yildirim A, Adam G, Cakir DU, and Karaman HI. Myelin basic protein and ischemia modified albumin levels in acute ischemic stroke cases. Pak J Med Sci. 2015;31(5):1110-4. DOI: 10.12669/pjms.315.7702.
25. Demirci B, Karakılıç ME, Coşkun A, et al. The brain ischemic volume correlation with the ischemic modified albumin level. Bagcilar Medical Bulletin. 2021.
26. Ahn JH, Choi SC, Lee WG, and Jung YS. The usefulness of albumin-adjusted ischemia-modified albumin index as early detecting marker for ischemic stroke. Neurol Sci. 2011;32(1):133-8. DOI: 10.1007/s10072-010-0457-4.
27. Nayak AR, Kashyap RS, Kabra D, Purohit HJ, Taori GM, and Daginawala HF. Prognostic significance of ischemia-modified albumin in acute ischemic stroke patients: A preliminary study. Ann Neurosci. 2011;18(1):5-7. DOI: 10.5214/ans.0972.7531.1118103.
28. Roy D, Quiles J, Gaze DC, Collinson P, Kaski JC, and Baxter GF. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart. 2006;92(1):113-4. DOI: 10.1136/hrt.2004.049643.
29. Lee P and Wu X. Review: modifications of human serum albumin and their binding effect. Curr Pharm Des. 2015;21(14):1862-5. DOI: 10.2174/1381612821666150302115025.
30. Jena I, Nayak SR, Behera S, et al. Evaluation of ischemia-modified albumin, oxidative stress, and antioxidant status in acute ischemic stroke patients. J Nat Sci Biol Med. 2017;8(1):110-13. DOI: 10.4103/0976-9668.198346.