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Original Article

Ischemia Modified Albumin, Serum Uric Acid and Serum Albumin as a Biomarkers of Oxidative Stress in Acute Ischemic Stroke

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ABSTRACT

Background: Stroke is one of the leading causes of mortality and long-term disability. Prompt diagnosis and treatment of stroke are crucial for a better outcome. A blood test, which serves as a biomarker in rural areas, will help immediately transfer patients to a hospital for thrombolytic therapy.

The Aim of the work: To evaluate the role of Ischemia modified albumin [IMA] level, uric acid and serum albumin in early diagnosis of acute ischemic stroke [AIS].

Patients and Methods: This study is a case-control comparative study done on thirty ischemic stroke patients presenting with acute stroke within 8 hours of stroke onset from onset of symptoms evaluated at Al-Zhraa University Hospital, and thirty healthy individuals matched for sex and age with patients, serum albumin, serum uric acid, and IMA were measured both on admission and 48 hours after admission.

Results: Patients exhibited significantly lower serum uric acid levels [2.98 ± 0.49 mg/dL vs. 5.66 ± 0.87 mg/dL, $p < 0.001$] and serum albumin levels [3.23 ± 0.90 g/dL vs. 5.12 ± 0.70 g/dL, $p < 0.001$] compared to controls. Moreover, patients demonstrated significantly higher IMA levels [20.55 [15.9 - 38.6] mg/dL vs. 14.85 [11.2 - 16.8] mg/dL, $p < 0.001$] compared to controls. Notably, lower serum uric acid levels [$r = -0.860$, $p = 0.008$] and lower serum albumin levels [$r = -0.516$, $p = 0.018$] were significantly associated with more severe stroke outcomes, as assessed by the modified Rankin scale [MRS].

Conclusion: The IMA and oxidative stress biomarkers may be sensitive and rapid biomarkers for screening of early ischemic stroke.

Keywords: Acute Ischemic Stroke; Ischemia Modified Albumin; Uric Acid; Albumin; Oxidative Stress.

INTRODUCTION

Stroke is ranked as the second leading cause of death worldwide. Thus, stroke is a disease of immense public health importance with severe economic and social consequences [1]. Fast and accurate stroke diagnosis is crucial for immediately applying the right therapy to patients. In addition, clinical situations that imitate the signs and symptoms of stroke may also impede the rapid diagnosis and treatment of stroke victims. Therefore, it is of value to discover non-invasive tests that aim to quickly distinguish stroke from stroke mimics and distinguish ischemic from hemorrhagic stroke [2].

Computed Tomography [CT] scan is the first choice for screening suspected stroke, which can distinguish intracranial hemorrhage and nonvascular lesions. However, it is difficult to find and diagnose the disease early [3]. Magnetic Resonance Imaging [MRI] is not available in all medical facilities managing emergency cases. For this reason, it is thought that serum biomarkers could be used for early diagnosis of acute ischemic stroke [4].

Oxidative stress plays an essential role in the pathogenesis of ischemic brain injury. The role of oxidative stress in ischemic stroke pathogenesis cannot be overstated, as it fuels the cascade of cellular injury culminating in potentially irreversible brain damage. Deprived of oxygen during ischemia, metabolic dysregulation results in an overproduction of reactive oxygen species [ROS]. These potent pro-oxidants trigger deleterious chain reactions, inflicting widespread damage on cellular biomolecules. This oxidative onslaught significantly contributes to cell death, further aggravated by the reperfusion paradox upon blood flow restoration. Thus, oxidative stress emerges as a central mediator of ischemic injury, dictating the fate of vulnerable tissues and potentially influencing the severity of neurological sequelae [4]. Brain tissues are prone to the harmful effects of free radicals because the brain cellular membrane lipids are very rich in polyun-saturated fatty acid side chains, which are especially sensitive to free radical attacks [5]. A growing body of investigation supports the potential role of ischemia-modified albumin [IMA] as a marker of brain ischemia [6].

Albumin is a single-chain polypeptide with 585 amino acids. It has a heart-shaped structure with three domains [I, II, and III]. The N-terminal end [the beginning of the chain] resides in domain I and is particularly susceptible to modifications under ischemic conditions. However, the exact mechanisms for IMA formation are still under investigation including oxidation by ROS, fatty acid adduction, and proteolysis.

To the best of our knowledge, this study is a valuable contribution to the field of stroke research. The findings of the study have the potential to improve the diagnosis and treatment of stroke, which could lead to better patient outcomes. The present study aims to evaluate the role of oxidative stress biomarkers and IMA in early screening of AIS.

PATIENTS AND METHODS

This study is a case-control comparative study done on thirty ischemic stroke patients presenting with acute stroke presented within 8 hours of stroke onset symptoms evaluated at Al-Zhraa University Hospital, and thirty healthy individuals matched for sex and age with patients, measuring serum albumin on admission, serum uric acid on admission and IMA on admission and after 48 hours.

Written informed consent was taken from all participants after an explanation of the study. This study is a case-control comparative study on thirty ischemic stroke patients with acute stroke who were evaluated at Al-Zhraa University Hospital between June 2020 and July 2021.

The study included two groups. The patient group included thirty patients diagnosed with AIS presented within 8 hours of stroke onset symptoms. The control group consists of thirty healthy individuals matched for sex and age with patients. They had the same demographic characteristics.

Inclusion criteria: Patients diagnosed as AIS within 8 hours of symptoms onset.

Exclusion criteria: [1] Ischemic stroke after 8 hours from onset, [2] Hemorrhagic stroke, and [3] Associated systematic diseases such as liver, cardiac, especially ischemic heart diseases, kidney, infections, cancer, history of thyroid disease and uncontrolled DM.

Methodology

All individuals were subjected to complete history taking, full general examination, full

neurological examination, especially for signs of cerebrovascular stroke [paresis, paralysis, loss of sensation, abnormal speech and balance abnormality], National Institute of Health Stroke Scale [7] [NIHSS] was recorded for all cases at admission, to measure stroke severity ranging from 0-42. A modified Rankin Scale was done on all patients after three months of symptoms to evaluate short-term post-stroke disability ranging from 0-6 [8].

Patients received routine institutional care according to their diagnosis blinded to the IMA results. In addition, levels of IMA were measured using the commercial Enzyme-Linked Immunosorbent Assay [ELISA] kit. This kit uses enzyme-linked immune sorbent assay [ELISA] based on the Biotin double antibody sandwich technology to assay the Human Ischemia Modified Albumin [IMA].

Laboratory investigations included complete blood count, liver function tests, especially serum albumin [N=3.4- 5.4 g/dL], serum uric acid [N= 3.5- 7.2 mg/dL], and [2.6 and 6.0 mg/dL] in females. All were done on admission, and IMA was done on entry and after 48 hours.

Sampling method: Patients were eligible for inclusion if they were 18 years of age or older, had a diagnosis of acute ischemic stroke confirmed by computed tomography [CT] or magnetic resonance imaging [MRI], and presented within 8 hours of stroke onset. Healthy controls were recruited from the community and were matched for age and sex with patients.

Statistical analysis: Data were analyzed using the Statistical Package for the Social Sciences [SPSS] software version 23. Continuous variables were compared using the t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test. Pearson's correlation coefficient was used to measure the association between IMA levels and serum albumin levels.

RESULTS

Demographic and clinical characteristics

A comparative analysis of age and sex distribution between patients and controls revealed no statistically significant differences [Table 1]. Brain computed tomography [CT] scans upon admission demonstrated ischemic findings in 53.3% of patients, with the remaining 46.7% exhibiting no abnormalities [Figure 1].

Biochemical parameters

Serum uric acid and serum albumin levels exhibited significant reductions in the patient group compared to the control group [Table 2].

IMA

IMA levels showed a remarkable increase upon admission in the patient group relative to the control group **[Table 3]**. Also, it shows that there is no statistically significant difference between patients' group and control group as regard IMA after 48 hours.

Diagnostic accuracy

Receiver operating characteristic [ROC] curve analysis identified a cut-off point of >15.8 for IMA to effectively differentiate between patients and controls. This cut-off point yielded a sensitivity of 80%, a specificity of 66.67%, and an area under the curve [AUC] of 0.778 [Figure 2 and Table 4].

Associations with stroke severity

A highly significant negative correlation emerged between serum uric acid levels and MRS scores, indicating that lower serum uric acid levels were associated with more severe stroke outcomes [Table 5]. Similarly, a significant negative correlation was observed between serum albumin levels and MRS scores, further supporting the association between biochemical parameters and stroke severity. Additionally, a statistically significant positive correlation was found between IMA levels on admission and NIHSS scores [Table 6]. This correlation suggests that higher IMA levels may be indicative of more severe stroke presentations.

Correlation between Ischemia Modified Albumin and age, number of hours from stroke onset and Modified Rankin Scale [MRS]

The study shows that there is no statically significant relation between IMA and age, blood pressure, Number of hours from stroke onset or MRS values [**Table 7**].

Table [1]: Demographic data of the patients' group and control group as regarding age and sex distribution

		Control group	Patients group	Test value	P-value
		No. = 30	**No. = 30**		
Age [years]	Mean ± SD	55.83 ± 12.94	61.37 ± 10.97	-1.787	0.079
	Range	40 – 80	41 – 88		
Sex	Female	22 [73.3%]	16 [53.3%]	2.584	0.108
	Male	8 [26.7%]	14 [46.7%]		

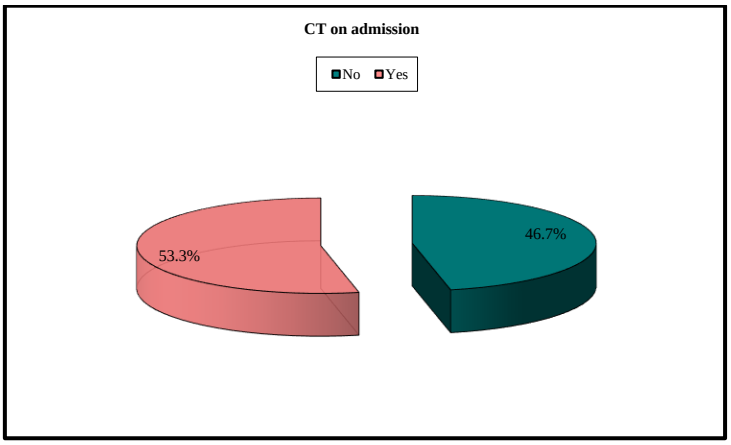

Figure [1]: Demographic data of the patients' group regarding brain CT on admission

Table [2]: Comparison between patients and control groups as regarded serum uric acid and serum albumin values on admission

		Control group	Patients group	Test value	P-value
		No. = 30	**No. = 30**		
Serum Uric acid on admission [mg/dl]	Mean ± SD	5.66 ± 0.87	2.98 ± 0.49	14.795	**< 0.001**
	Range	4.5 – 7.5	2.25 – 4		
Serum albumin on admission [mg/dl]	Mean ± SD	5.12 ± 0.70	3.23 ± 0.90	9.124	**< 0.001**
	Range	4 – 6.5	0.3 – 4.9		

Table [3]: Comparison between patients and control groups as regard IMA values on admission and after 48 hours

IMA		Control group	Patients group	Test value	P-value
		No. = 30	**No. = 30**		
On admission	Median [IQR]	14.85 [11.2 – 16.8]	20.55 [15.9 – 38.6]	-3.704	**< 0.001**
	Range	9.04 – 140.6	9.97 – 119.9		
After 48 h.	Median [IQR]	14.85 [11.2 – 16.8]	13.45 [9.54 – 16.2]	-1.050	0.294
	Range	9.04 – 140.6	1.66 – 21.3		

Table [4]: Sensitivity and Specificity of IMA

Parameter	AUC	Cut of Point	Sensitivity	Specificity
IMA	0.778	>15.8	80.0	66.67

Table [5]: Association between serum uric acid, serum albumin on admission and modified Rankin scale [MRS]

		MRS		Test value	P-value
		Moderate	**Severe**		
		No. = 12	**No. = 18**		
Serum Uric acid on admission [mg/dl]	Mean ± SD	3.16 ± 0.45	2.70 ± 0.41	-2.860	**0.008**
	Range	2.35 – 4	2.25 – 3.37		
Serum albumin on admission [mg/dl]	Mean ± SD	3.54 ± 0.78	2.77 ± 0.89	-2.516	**0.018**
	Range	2.5 – 4.9	0.3 – 3.8		

Table [6]: Correlation of IMA on admission and after 48 hours with NIHSS score

		IMA on admission	IMA after 48 hours
NIHSS score	**r**	0.377	0.254
	p-value	**0.040**	0.175

Table [7]: Correlation between Ischemia Modified Albumin and age, Number of hours [[N.H.] from stroke onset and Modified Rankin Scale [MRS]

	IMA on admission	
	r	**P-value**
Age	0.289	0.121
Number of hours	0.091	0.631
MRS	0.108	0.569

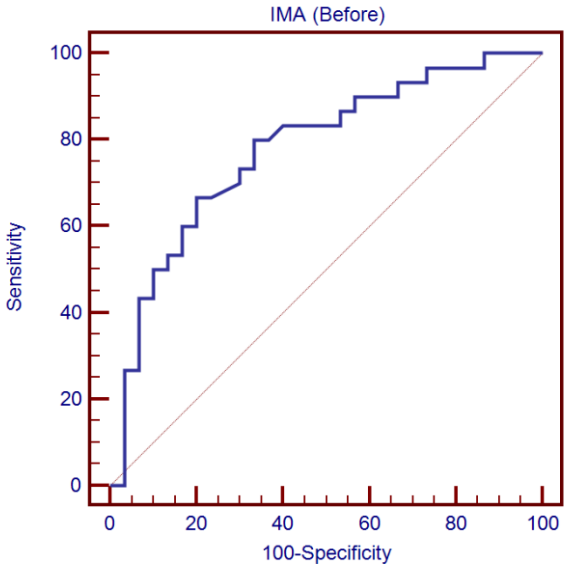

Figure [2]: ROC curve of IMA as a predictor of ischemic stroke

DISCUSSION

Accurate and rapid diagnosis of stroke is necessary to make prompt decisions in therapy. Our study shows a non-significant difference between patients and control regarding age, with a mean age of 55.8 years in patients. In addition, the present study indicated that 30% of the patient's group had diabetes mellitus, 40% had hypertension, and 6.7% had diabetes and hypertension. Our results are in agreement with a study by **Arboix *et al.*** [9] who reported that the most frequently observed co-morbidity and risk factors in the AIS patients were hypertension with a rate of 54% and diabetes mellitus at 22.6%.

In the present study, neuro imaging CT scan has no ischemic finding in about 46.7% of patients, while about 53.3% have early ischemic changes on 1st hours of admission. In agreement with our results, who reported that CT is the method of choice to rule out intracerebral bleeding but has low sensitivity and specificity in early diagnosis of acute ischemic stroke [3].

In the present study, serum uric acid and serum albumin levels are significantly decreased in the patients' group than in the control group [P < 0.001]. In addition, a study by **Menon *et al.*** [10] have found that serum uric acid and serum albumin values were significantly decreased in AIS cases compared to controls [P=0.0001].

IMA level which collected in the within 8 hours of stroke onset in the present study was significantly higher in stroke patients as compared to controls as IMA is elevated in the acute phase of stroke [P-value< 0.001]. Such findings are in agreement with a case-control study done by two studies [6, 11], which reported that IMA levels are higher in patients with acute ischemic cerebrovascular diseases than healthy individuals.

In the present study, we assessed the serum level of IMA after 48 hours. Our results showed no statistically significant difference between the patient and control groups regarding IMA after 48 hours of admission since IMA has a short half-life and re-turning to baseline values within 6–12 hours. In agreement with our results, **Jena *et al.*** [11] reported that IMA was elevated in the acute phase of stroke and had a gradual graded decline over one week. Furthermore, our results align with **Nayak *et al.*** [12] who observed that IMA level decreases in the follow-up AIS samples [at 24, 48 and 72 hrs] compared to admission value.

Our study found a high significant negative correlation between serum uric acid level on admission and short neurological outcome evaluated by MRS with a p-value of 0.008. Thus, higher levels of entry can predict good outcomes for patients. In addition, the study of **Jena *et al.*** [11] is in agree with our finding who reported that higher levels of uric acid in patients with AIS reveals better outcome.

The present result shows a significant negative correlation of serum albumin level on admission and MRS with a p-value of 0.018. Thus, higher levels of entry predict good outcomes for patients. This result is in line with **Dziedzic *et al.*** [13] who reported that patients with poor outcomes had significantly lower serum albumin levels than patients with good outcomes. Correspondingly, our study shows a positive correlation between IMA on admission and stroke severity evaluated by NIHSS score. Such findings agreed with **Jena *et al.*** [11] who reported that there was a significant correlation between IMA and NIHSS [p-value < 0.05] in patients diagnosed as acute ischemic infarction on admission.

In the present study, there is non-significant negative association between IMA with serum uric acid [*P*-value 0.268] and serum albumin [*P*-value 0.234], but this correlation was not significant. Such findings are partially agreed with **Jena *et al.*** [11]**,** who reported a significant negative correlation between IMA and serum albumin [P < 0.05]. These results could be due to, Jena study was conducted on larger number of cases and controls than our study, further investigations and larger samples are required for more support to our result.

Furthermore, a systematic review and meta-analysis by **Mangoni *et al.*** [14] have shown the presence of significant differences in serum IMA concentrations between patients with specific stroke subtypes and non-stroke controls. Additional research is warranted to investigate the relationships between IMA generation and the extent of brain damage, clinical progress, long-term outcomes, and specific patient characteristics such as gender and ethnicity. Only then can the clinical utility of routine IMA measurements be appropriately determined.

Additionally, A prior systematic review and meta-analysis evaluated the diagnostic performance of IMA in six AIS studies, yielding a sensitivity of 0.80 [95% CI: 0.69-0.88], a specificity of 0.80 [95% CI: 0.71-0.87], and an area under the receiver operating characteristic curve [AUC] of 0.86 [95% CI: 0.83-0.89] [15].

Limitation of the study: Our included population were not based on sample size calculation, and the numbers of patients in our study was limited. In addition, ischemic stroke patients should be compared with hemorrhagic stroke to know if there is the cut-off point that differentiates between ischemic and hemorrhagic insult.

Conclusion and recommendations: Our results in this study showed decreased serum uric acid and serum albumin levels in stroke patients. In contrast, an increased level of IMA in the study population further supports that an imbalance in oxidant and antioxidant status plays a vital role in the pathophysiology of ischemic brain injury. As an oxidative stress biomarker, IMA could be used as a rapid and easy diagnostic tool in AIS. Studies with longer duration of follow-up should be conducted to demonstrate the prognostic utility of a biomarker; a larger sample and prospective design are required.

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