Serum Galectin-3 and Poor Functional Outcome in Acute Ischemic Stroke

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Conflict of Interest: None declared.

Funding: No funding sources.

Abstract

Objective: The current study aimed to investigate the role of serum Galectin-3 level asa prognosticator of short-term outcome in acute ischemic stroke (AIS). Patient and methods: Ninety cases with former acute ischemic stroke (36 males and 54females)werepresented in this prospective cohort study. Stroke severity was assessed on admission by the National Institutes of Health Stroke Scale (NIHSS), and functional results were evaluated after 12 weeks of admission by Modified Rankin Scale (mRs). Galectin-3 levels were assessed using the ELISA technique.

Results: The results revealed that the association between Galectin-3 level and diabetes mellitus, hypertension, obesity, cardiac diseases, stroke severity, and poor functional outcome were significantly different. The relation regarding Galectin-3 levels and the size of the infarction showed a significant positive correlation. Binary logistic regression analysis of neurological outcome with associated risk factors demonstrated that diabetes mellitus, elevated serum Galectin-3 level, NIHSS, and mRS scores were the most significant risk factors for predicting deterioration and short-term outcome after ischemic stroke after adjustment of other confounding variables.

Conclusion: serum Galectin-3 is a prognostic biomarker of poor outcome after acute ischemic stroke.

Keywords: ischemic stroke, serum galectin-3, biomarker, functional outcome.

Tob Regul Sci.™ 2021;7(6-1): 7425-7435

DOI: doi.org/10.18001/TRS.7.6.1.64

Background

Stroke is considered a heterogeneous and multifactorial disease that affects people worldwide. It is considered the largest precursor of disability and mortality worldwide [1]. It is considered the second most frequent precursor of mortality in the world and comes in third place in the most common disease in developed countries [2]. Ischemicstroke is caused mainly by focal hypoperfusion, thrombosis, and embolism, the previous conditions can induce interruption and brain function is affected by a reductionin cerebral blood flow (CBF). At rest, the brain receives about a fifth of the heart's bloodflow [3], The brain and even neurons are highly sensitive to ischemia, although 20% ofcardiac outcome was received by the brain at rest conditions, such ischemic condition even in brief periods can induce a complicated sequence

causing cerebral damage permanently[3].

Galectin-3 is a lectin subtype, a group of proteins that affect cell viability by carbohydrate-binding [4]. Galectin-3 has other synonyms, carbohydrate-binding protein 35 or Mac-2, which binds specifically to galactoside sugar [5], A research indicates that expression of Galectin-3 in the astrocytes and ependymal cells had a potential effect on the movement of neuroblasts in the course of brain development [6]. Galectin-3 expression is elevated after brain injury mainly in microglial cells besides astrocytes and oligodendrocytes [7]. **Jagodzinski and colleagues** reported in their study of multivariable-adjusted models that ischemic stroke event after a follow-up for 15 years was weakly correlated with Galectin-3. Despite the results that Galectin-3 from hematopoietic cells can lead to insulin resistance cellularly and even systemically [8]. Another study on type 2 diabetes mellitus on 282 Chinese patients did not show a significant association between elevated Galectin-3 level and stroke [9].

The goal of this study was to determine the relationship between blood Galectin-3 levels and neurological deterioration as well as functional outcomes in patients with their first-ever case of AIS.

Patients and methods:

Between September 2018 and September 2019,at intensive care and stroke units, Neurology Department, Zagazig University Hospitals, we conducted this study. All patients or their relatives were given written permission to participate in the study. TheZagazig University Faculty of Medicine's research board gave its approval to this work.

Ninety patients were conducted with first-ever cerebrovascular AIS, who were diagnosed according to the World Health Organization (WHO) criteria in this prospective-cohort study [8], of not more than 72 hours duration. Patients who suffered from hemorrhagic stroke (intracerebral or subarachnoid hemorrhage), and central nervous system disease other than acute cerebral arterial infarction, patients with metabolic emergencies, patients with a history of head injury, patients with chronic kidney or liver disease were excluded.

Ethical consideration:

Patients were represented to history taking, neurological and general examinationwith evaluation of stroke severity using NIHSS on admission.

Assessment of baseline vascular risk factors:

Diagnosis of vascular risk factors was assessed by laboratory findings and history. Patients are considered hypertensive if their SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHgor receiving antihypertensive medications according to WHO guidelines [9]. Also, patients are considered diabetic when their fasting venous plasma glucose levels ≥ 7.0 mmol/l, or plasma glucose ≥ 11.1 mmol/l 2 h after a 75g oral glucose intake, or receivingantidiabetic medications [9].

Dyslipidemia was determined as those having previous diagnosis of dyslipidemia, the use of lipid lowering medication or abnormal fasting lipid profile as follows: Total cholesterol level > 200 mg/dL, LDL ≥ 100 mg/dL, HDL <40 mg/dL or triglycerides level > 150 mg/dL [10].

A history of smoking was recorded with patients who smoke before the stroke eventby 3 months [9].

Patients with BMI ≥ 30 kg/m^2 considered obese [11].

Laboratory investigations:

Both routine and special laboratory investigations were performed at the department of clinical pathology. Routine laboratory analysis included complete blood count, random blood sugar (RBS), kidney and liver function tests, lipid profile, and Coagulation profile.

Special laboratory investigations for measurement of Galectin-3 serum level by 3 ml of venous blood drawn from all cases, within 72 h of stroke onset. The samples werecentrifuged and kept in serum after resting at room temperature for four hours forbloodclotting. Galectin-3 levels were evaluated by double antibody sandwich ELISA technology.

Radiological investigations:

All patients were subjected to CT and MRI to confirm the diagnosis of acute stroke.

Follow up after 12 weeks for:

Evaluation of stroke severity by NIHSS which was categorized according to Hage,2011 [12] into Mild stroke severity if NIHSS less than 6, moderate stroke severity if NIHSS 6-15, moderate to severe stroke if NIHSS 16-20, severe stroke if NIHSS 21-42.

Functional outcome assessment (follow up) after 12 weeks using:

The scale of mRs formed of 6 grades, from 0 to 6, no symptoms (0) and severe disability (5), and death (6). A score on the mRS of 0-2 denotes a good outcome whilea score ≥ 3 denotes a poor outcome [13].

Statistical analysis:

Data coding and input were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA), a statistical package for social sciences. An alpha level below 0.05 was considered for statistical significance. Quantitative data was described using mean and standard deviation (SD), and qualitative data was presented using number and percentage. Quantitative data was examined using student's t-tests to determine statistical differencesThese tests were employed for quantitative variables that were notnormally distributed:. Nonparametric Mann–Whitney (MW) and Kruskal–Wallis (KW)tests. Pearson's correlation was utilized to examine the correlation between quantitativedata. To be deemed statistically significant, P values of less than or equal to 0.05 . Analysis of test findings and the comparison of different testing procedures was made possible by the construction of a receiver operating characteristic curve (ROC) curve.

Results:

Ninety cases were subjected to the study (54 females and 36 males) with first-ever cerebrovascular AIS of not more than 72 hours duration with age ranging from (58 years to 66years). The mean age was 62 ± 9 years.

The relation between Galectin-3 level and ischemic stroke risk factors (Diabetes mellitus, cardiac disease, obesity, and hypertension) was statistically significant **(Table1).**

Galectin-3 and diastolic blood pressure, size of infarction, NIHSS (at admission), NIHSS after 12 weeks of stroke onset, mRs and mRs 12 weeks were correlated significantly with a high statistical significance (p<0.001), negative a statistical correlation with Glasgow coma scale at admission and after 12 weeks from admission (p=0.001). **(Table2)**

There was a statistically significant association between serum Galectin-3 level andstroke severity, the poor functional outcome as assessed by NIHSS, mRS score respectively after 12 weeks of stroke onset. **(Table 3)**

Binary logistic regression analysis of neurological deterioration and poor outcome demonstrated that diabetes, high NIHSS score, poor mRS, and elevated serum Galectin-3 level were the most independent important predictors for neurological deterioration and poor functional outcome after 12 weeks of stroke onset with adjustment of other confounding study variables. **(Table 4)**

Galectin-3 can be used to predict mortality at cut-off value >13.28, with high statistical significance (p<0.001), an area under curve 0.936, sensitivity 100%, and specificity of 71.05% (Table 5).

Table 1: The relationship between serum Galectin-3 level and ischemic stroke risk factors among thestudied AIS patients.

Serum Galectin-3, ng/ml.			Test	P-value	Median IQR
Gender	Female	15.24	(12.34-17.21)	-0.405 *	0.685
	Male	13.58	(11.26-18.1)		
Diabetes mellitus	No	12.34	10.46-13.23	-6.456 *	<0.001¶
Yes		17.23	16.2-18.8		
Hypertension	No	11.26	10.34-12.45	-6.645 *	<0.001¶
Yes		16.38	15.24-18.36		
Smoking	No	15.44	(12.37-17.23)	-0.961 *	0.336
Yes		13.14	(11.26-16.78)		
Cardiac diseases	No	12.41	10.46-12.56	-6.553 *	<0.001¶
Yes		17.21	15.53-18.8		
Obesity	No	11.27	10.36-12.5	-6.457 *	<0.001¶
Yes		16.47	15.46-18.38		
Hyperuricemia	No	15.29	(12.475-17.355)	-0.902 *	0.367
Yes		12.9	(11.77-16.625)		
Dyslipidemia	No	13.96	(11.36-16.995)	-0.870 *	0.384
Yes		15.39	(12.42-17.92)		

* Compared using Mann Whitney test; ¶ = Significant

Table 2: Correlation between serum Galectin-3 level and continuous variables of the studied patients

Spearman's correlation	S. Galectin-3, ng/mL.	
	Correlation Coefficient	Sig.
Age	-0.151	0.155
Systolic BP	0.181	0.088
Diastolic BP	0.226	0.032
RBG	0.075	0.568
HB	-0.024	0.825
TLC	0.086	0.516
S.Creat	0.079	0.461
ALT	-0.163	0.125
AST	-0.155	0.144
T.Bilirubin	0.061	0.641
D.Bilirubin	0.106	0.420
TGS	-0.051	0.635
Cholest	-0.043	0.689
LDL	0.125	0.342
HDL	0.005	0.969
PLTs	0.118	0.370
INR	0.061	0.567
PTT	-0.050	0.642
GCS (at admission)	-0.482	<0.001*
GCS (after 12 weeks)	-0.351	0.001*
NIHSS (at admission)	0.528	<0.001*
NIHSS (after 12 weeks)	0.453	<0.001*
mRS (after 12 weeks)	0.711	<0.001*
Size of infarction	0.622	0.001

r = Correlation Coefficient

Table 3: Association between serum Galectin-3 level and stroke severity, functional outcome assessedby NIHSS score mRS.

S. Galectin-3, ng/mL			Test	PMedian	IQ range
Initial NIHSS	Moderate	15.89	(13.37-18.37)	2#	0.872
Moderate tosevere		17.48	(11.64-21.3)		
Severe		21.79	(12.5-23.57)		
NIHSS. after 12weeks	Minor	14.94	(11.47-16.46)	3#	0.04
	Moderate	16.47	(12.6-18.38)		
Moderate tosevere		14.7	(11.53-23.55)		

Severe		22.4	(22.1-26.6)		
Functional.	mRS 0-2(n=19)	15.24	(12.31-18.34)	-1.92*	0.05
Outcome	mRS 3 -5(n=41)	17.48	(13.25-22.47)		

P ≤ 0.05= significant P >0.05 Non-significant # KW test *MW testNIHSS: National Institutes of Health Stroke Scale
mRS: modified Rankin scale mRS (0-2) is good, (3-5) is poor

Table 4: Binary logistic regression analysis of neurological deterioration and poor functional outcomewith associated risk factors.

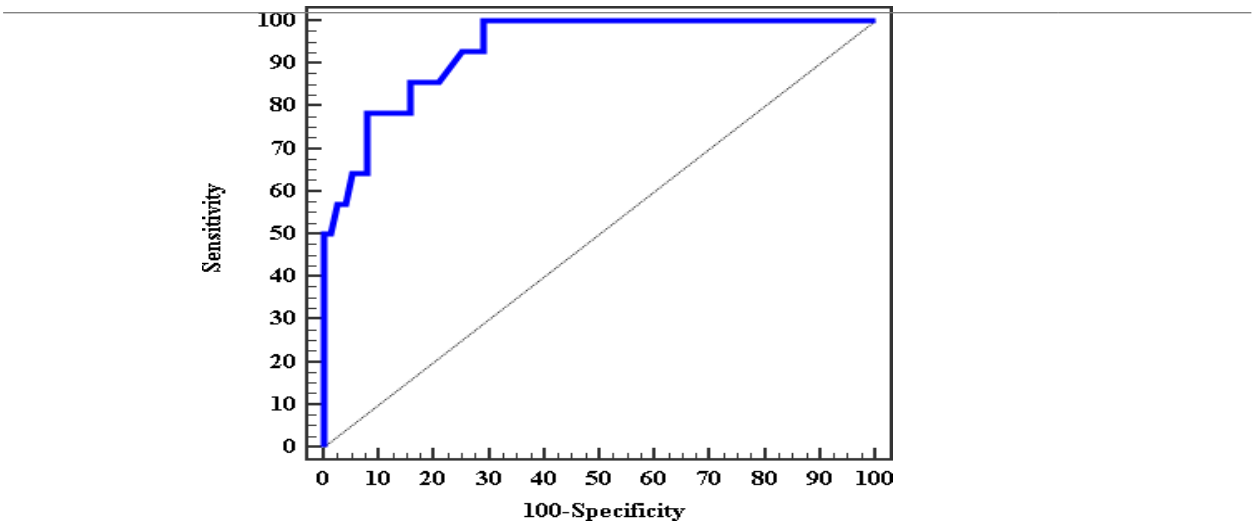
Covariates	Odds ratio	(95% CI)	Sig.
Age	0.910	0.76-1.09	0.305
Sex	0.263	0.003-24.946	0.565
DM	1.166	0.04-14.352	**0.022***
HTN	0.0003	0.0001-0.009	0.999
Smoker	0.690	0.015-31.274	0.849
Obesity	36.950	0.976-1399.035	0.052
Dyslipidemia	5.581	0.121-256.41	0.379
S.Galectin-3, ng/mL.	1.104	0.432-1.146	**0.008***
NIHSS	3.12	0.151-7.24	**0.032***
mRS	2.712	0.128-4.213	**0.014***
Size (medium vs small)	0.177	0.004-7.076	0.358
(large vs small)	0.226	0.008-6.137	0.377
Constant	1687.5		

*Significant, (CI) confidence interval

Table 5: Agreement (sensitivity, specificity) for Galectin-3 to predict mortality (n = 14 vs. 76)

Cut-off	Sensitivity % 95% CI	Specificity % 95% CI	PPV % 95% CI	NPV % 95% CI	AUC	95% CI	P
>13.28	100	71.05	38.9	100	0.936	[0.879 –0.992]	**<0.001***

Figure 1: The Area under the ROC curve (AUC) of initial serum Galectin-3 as a prognostic marker for neurological deterioration



Discussion

Stroke comprises a potential health problem. It comes in third place in precursors ofdeath behind cancer and heart disease and is assumed to be a significant stimulant of long-term disability as well [14]. Survivors of stroke were still at a high risk of death. As a consequence of clinical importance to the prediction of acute stroke outcome considered with potential medical priority. Nowadays, clinical variables including symptoms severity and aging are considered as vital outcome prognosis [15]. Galectin-3 was normally highly expressed in cerebral parenchyma [16] and CSF [17] after injury.The elevation of serum Galectin-3 was due to the breakdown of the blood-brain barrieras a result of ischemic stroke. Galectin-3 expression is related to the severity of the stroke, disability, and worse neurological outcome [18].

The current study purpose was to assess Galectin-3 serum levels of Galecyin-3 anditsrelation with severity of AIS and functional outcome as well.

Our study included 90 first-ever cerebrovascular AIS patients (60% were females while 40 % were males). Their mean age was 62 ± 9years with a range (58-66) years. We found that there was a statistically significant association between Galectin-3 serumlevel and ischemic stroke risk factor as diabetes mellitus and positive correlation with random blood sugar (RBS). Consistent with these observations, **Arora, and colleagues**
[19] and **Zeng and colleagues** [20] reported in a study that included hyperglycemic patients with stroke that Galectin-3 elevated levels were correlated with recurrence events and high risk of poor functional outcome. On the other hand, this finding mismatches with that of **Jin and colleagues** [21] who did not report any change in stroke probability with elevated Galectin-3 levels in cases with type 2 diabetes mellitus.This difference may be attributed to different study designs and different ethnicity. In addition, there was also a statistically significant correlation between serum level of Galectin-3 and history of hypertension, and both SBP and DBP measurements. In agreement with this finding, Galectin-3 was evaluated in 526 cases with incident ischemic stroke, by **Arora and colleagues** [19] who reported that the patients from the group corresponding to the highest Galectin-3 levels were remarkably more hypertensive, also **Dong and colleagues** [22] found a significant association between Galectin-3 and SBP but not with diastolic blood pressure. This difference may be due to different sample characteristics or due to fluctuations of the Galectin-3 level in different stroke stages.

According to the current study, the relation between serum Galectin-3 level and smoking were not significantly correlated, a finding that was opposite to the results of **Dong and colleagues** [22] that suggested a significant correlation between the highestlevels of Galectin-3 and history of smoking. This difference could be explained by thefemale predominance of our study patients who are fewer smokers than males. As regards dyslipidemia, Galectin-3 serum level and history of dyslipidemia were not significantly correlated. In contrast, **Dong and colleagues** [22] reported that higher quartiles of Galectin-3is are associated with an increase in LDL with no significance for TC, TG, and HDL, and also **Wang and colleagues** [23] found that increased Galectin-3 has been correlated with atherosclerosis. Obesity is considered an atherosclerotic risk factor and also, a health burden. Regarding obesity, the present study reported a highly statistically significant correlation between serum Galectin- 3level and

obesity, this finding was following **Arora and colleagues [19],** who suggested that Galectin-3 was elevated in cases with high BMI with stroke. Contrary to this result, **Dong and colleagues** [22] did not show a significant correlation between BMI and Galectin-3 expression.

In our results, the Galectin-3 level was highly significantly elevated among cases with a history of cardiac diseases (P<0.001). The evaluation of Galectin-3 was recommended by the American Heart Association guidelines to help in risk classification in heart failure (HF) cases **[5].** Galectin-3 has independent relation with mortality in HF **[24]** and can predict mortality precursors **[25].** The galectin-3 level was elevated after acute myocardial infarction in blood and cardiac tissues, this could suggest an inflammatory role before fibrosis and remodeling take place **[26].** IncreasedGalectin-3 level is considered a cardiac fibrosis marker, which is correlated with an elevated risk of HF and also mortality **[27]. Edsfeldt and colleagues** [28] reported that the Galectin-3 level had an elevated incidence of stroke, also **Chen and colleagues** [29] found that cases with atrial fibrillation which is considered a stroke risk factor, had increased Galectin-3 levels. Galectin-3 was also significantly correlated with elevated CHA2DS2-Vasc scores, and **Arora and colleagues [19] Sano and colleagues [30]** found a significant correlation between Galectin-3 level and cardiovascular risk factorof ischemic stroke.

In our present study, the main findings were that Galectin-3 levels were noticed to be high in acute ischemic stroke and elevated Galectin-3 levels were associated with the severity of stroke. People with higher Galectin-3 levels had a high likelihood of ischemic stroke. It has been found that median serum Galectin-3 levels of the studied patients at the time of admission was 11.93ng/ml with an IQ range (7.42-13.8).

In our study, the results revealed a statistically significant elevated Galectin-3 levelin AIS cases who had a severe stroke as assessed by NIHSS (at admission and after 12 weeks of follow up), moreover, Galectin-3 level was positively correlated with NIHSS score. This is in agreement with **Zhuang and colleagues** [31] who reported that NIHSS score was associated with Galectin-3 levels, as increased Galectin-3 levels were associated with prognosis at discharge and stroke severity at admission. Also, **Dong and colleagues** [22] suggested that Galectin-3 and Galectin-1 were upregulated in AIS cases compared to control. The galectin-3 level was correlated with the severity of AISindicated by NIHSS and infarction volume, and **He and colleagues** [32] reported that serum levels of Galectin-3 serum levels were significantly increased in the AIS cases with an unfavorable outcome compared to cases with a favorable outcome.

Our study results reported that AIS patients who had poor functional outcomes as assessed by mRS (mRS score 3-5) had a significantly increased Galectin-3 level than those with favorable outcome (mRS score 0-2), and there was a positive correlation between functional outcome as assessed by mRS after 12 weeks of admission and Galectin-3 levels. Matching with this result, **Dong and colleagues** [22] found that serum Galectin-3 was increased significantly in cases with a poor outcome indicated bymRS scores than in cases with a good outcome, also **Wang and colleagues** [23] in a study conducted on 3082 cases with AIS, the primary outcome was a collection of majordisability or death at 3 months after stroke as increased Galectin-3 levels were independently correlated with an elevated risk of major disability or death, presuming that Galectin-3 considered a prognostic factor for ischemic stroke with poor outcome,

and also with **Zhuang and colleagues [31]** in their study of ischemic stroke reported that elevation in Galectin-3 levels was correlated with the severity of stroke at admission and increase Galectin-3 levels were correlated with prognosis at discharge and stroke severity at admission.

Given our results, we can conclude that there is a significant positive association between serum Galectin-3 level and neurological deterioration and poor functional outcomes. We recommend that specialists should consider adding the use of Galectin-3 serum level to their routine admission testing in patients with AIS since it is significantly correlated with vascular risk factors, the severity of AIS and it is a usefulbiomarker for prediction of early neurological deterioration of acute ischemic stroke.

Further studies were recommended with a longer duration of follow-up and larger sample size, with measurement of Galectin-3 during this period to evaluate the variability and fluctuation in its value with time in stroke patients.

The study did not receive any financial support.The authors declared any conflicts of interest.

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