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ORIGINAL ARTICLE

The Role of Serum Matrix Metalloproteinase - 9 as a Prognostic Biomarker for Short-Term Outcome in Acute Ischemic Stroke

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ABSTRACT

Background: Stroke is a heterogeneous and multi-factorial disease that affects people globally. Matrix Metalloproteinase-9 is involved in blood-brain barrier breakdown, edema development, pro-inflammatory cytokine activation and destruction of myelin proteins are all connected to the pathogenic events that take place during an ischemic stroke., matrix metalloproteinase- 9 concentration is greatly related to infarct extension, neurologic impairments, and hemorrhagic transformation in individuals with ischemic stroke**. Objective:** We focused our research on improving individuals' outcomes after having an acute ischemic stroke by assessing the level of serum matrix metalloproteinase-9 24 hours after the stroke begins and the relation between Serum levels of matrix metalloproteinase-9, clinical severity, and ischemic stroke prognosis. **Methods:** This follow up prospective cohort research was conducted at Zagazig University Hospitals' Intensive Care Unit and Stroke Unit at the Neurology Department and Emergency Room. The study included 54 people experiencing their first acute ischemic stroke. Stroke severity and serum MMP-9 level were assessed on admission and following a 15-day follow-up. **Results:** Level of Serum MMP-9 was 1085.93 ng/ml with a range from 485 to 1544 ng/ml. Statistically significant positive correlation was found between serum MMP-9 and neurological severity as measured by NIHSS at admission and after 15 days. Also, there was a highly significant positive correlation between MMP-9 and functional outcome as assessed by mRS after 15 da ys follow up. The best cutoff of MMP-9 in prediction of large size infarction, that was ≥ 1042 Also, the best cutoff of MMP-9 in prediction of severe stroke was ≥ 1091 ng/ml. The best cutoff of MMP-9 in prediction of severe stroke after 15 days is ≥972.5 ng/ml. Among factors significantly correlated with baseline NIHSS, MMP-9, size of infarct, BI and mRS were significantly independently associated with baseline NIHSS among studied patients.**Conclusion:** Serum MMP-9 may act as potential prognostic factor predicting neurological severity and short term outcome in individuals with ischemic stroke.

Keywords: ischemic stroke, Matrix metalloproteinase 9, prognosis .

INTRODUCTION

Stroke is a heterogeneous and multi-factorial disease that affects people globally. It is considered as a primary cause of disability and death all over the world **[1].** Cerebrovascular events comprise of two types, ischemic and hemorrhagic, with the ischemic type more prevalent than hemorrhagic as it accounts for 85% of all strokes **[2].** Only recombinant tissue plasminogen activator is highly advised for acute ischemic stroke treatment. However, only a small percentage of patients actually meet the requirements for recombinant tissue plasminogen activator administration. Therefore, studying the causes and metabolic impairments that occur inside the area of brain infarction after an acute ischemic stroke is recommended. This demonstrate how important to find a reliable biomarker that could cross blood brain barrier

and help in the early detection of acute ischemic stroke **[3]**. Enzymes that degrade the matrix include matrix metalloproteinases. which are implicated in various pathophysiology processes such as systemic inflammation, atherosclerosis, and neurological disorders **[4].** These proteolytic enzymes, which ordinarily rebuild the extracellular matrix, are members of a family that binds zinc. Type IV collagen, laminin, and fibronectin, are considered the main constituents of the basal lamina surrounding cerebral blood vessels, and are selectively attacked by matrix metalloproteinase-9 **[5]**.MMP-9 has a an important pathogenic role thorough the acute phase of ischemic stroke, involving the destruction of the blood-brain barrier, the occurrence of edema, the activation of pro-inflammatory cytokines (like tumor necrosis factor-a and interleukin-1b) , and the breakdown of myelin proteins as well **[6]**.The elevated serum level of MMP-9 is strongly related to size and progression of brain infarct, neurological impairment and hemorrhagic transformation in subjects having acute ischemic stroke **[7,8]** and its inhibition is of potential therapeutic roles **making it as** a promising risk and prognostic biomarker of ischemic stroke **[9,10].**

This research's objective was to improve course and prognosis of patients with ischemic stroke through measuring levels of serum matrix metalloproteinase-9 within 24 hours of the stroke beginning, and after 15 days of follow up and its relation to both neurological impairment and short term functional outcome.

SUBJECTS AND METHODS

This prospective cohort study was done on fifty four subjects 23 male , 31 females who presented for the first time with acute ischemic stroke and were hospitalized in emergency Unit and stroke unit of Neurology Department of zagazig university hospitals from November 2019 to March 2021.Standard protocol approvals, registrations, and patients' consents were authorised by institutional review board number (ZU-IRB 5456-7-7-2019) , Faculty of medicine, Zagzig University .The following criteria were fully met by each participant in the study, inclusion criteria included age more than 18 years**.,** on first neurological examination, a focal neurological deficit lasting longer than 24 hours, first ever ischemic stroke and CT scan and /or MRI images of the brain display signs of recent cerebral ischemia. We excluded hemorrhagic stroke**,** severe systemic illness or any other medical problems that may increase matrix metalloproteinase-9 level, regular use of specific medications which might have an impact on MMP-9 level e.g. tetracycline derivatives such as minocycline or doxycycline, non-steroidal anti-inflammatory drugs, or statins such as atorvastatin or pravastatin, recent myocardial infarction, unstable angina, acute heart failure and pregnancy and postpartum. Clinical assessment included detailed medical history, complete neurological assessment and comprehensive physical examination. The degree of awareness, stroke severity were evaluated by Glasgow Coma Scale (GCS), and National Institutes of Health Stroke Scale(NIHSS), follow-up, and short-term outcome of stroke were all evaluated using the following scales:Modified Rankin Scale (mRS), and the Barthel Index (BI).Level of consciousness was evaluated using the Glasgow Coma Scale (GCS).The severity of the stroke was evaluated at admission as well as within 15 days later (second visit) using National Institutes of Health Stroke Scale (NIHSS) **[11].**Functional outcome was evaluated using modified Rankin Scale(mRS) and Barthel Index (BI) after 15days of follow up .Comprehensive standard laboratory testing included complete blood count, liver function tests, renal function tests, and a random plasma glucose level, lipid profile and coagulation profile.Measurement level of serum matrix metalloproteinase-9 using enzyme-linked immunosorbent assay.Cardiovascular examinations, such as 12-Lead ECG and echocardiography and carotid doppler ultrasonography. Radiological investigations including plain CT scan /and or MRI brain with measurement of infarct size. All patients, who were hospitalized, underwent care in accordance with the Neurology Department's Intensive Care Unit and stroke unit protocols. In the first day following a stroke, everyone was observed for blood pressure, temperature, blood glucose levels, and blood gases.

Statistical analysis: SPSS 22.0 for Windows (IBM 2013) was used to analyze all of the data. The mean, standard deviation, and median (range) were used to convey continuous data, whereas a number (%) was used to express categorical variables. We compared percentages of categorical variables using the Chi-square ($\chi 2$) test .We take the (+) sign as a sign of a direct correlation, where an increase in the frequency of the independent causes an increase in the frequency of the dependent, and the (-) sign as a sign of an inverse correlation, where an increase in the frequency of the independent causes a decrease in the frequency of the dependent. We also take values close to 1 as signs of a strong correlation and values close to 0 as signs of a weak correlation. To find predictors of post-stroke worsening, a forward stepwise logistic regression analysis was used. Every test had two sides. P values between 0.05 and 0.01 were classified as statistically significant (S), highly statistically significant (HS)respectively and non-significant (NS) if $P \geq 0.05$.

RESULTS

Fifty -four ischemic stroke patients were recruited in this research, of which ,57.4% were females. Age ranged from 50 to 85 years with mean 64.2 years. Concerning associated risk factors, 57.4%, 79.6%, 40.7%, 35.2% and 18.5% had diabetes, hypertension, cardiac disease, dyslipidemia and migraine respectively. About 38.7% of studied females were on contraceptive pills. Smokers and obese represented 37% and 46.3% of studied patients. Mean MMP-9 was 1085.93ng/ml with a range from 485 to 1544 ng/ml (table 1). A statistically significant improvement in NIHSS mean score after 15 days as compared to baseline value was reported by our results. On the other hand, there is significant increase in mean score of GCS (there was statistically significant difference in both mean scores of NIHSS and GCS at admission and after 15 days of follow up denoting improvement of stroke severity) (table 2).The MMP-9 serum level had a statistically significant positive connection with the NIHSS-measured severity of stroke at admission, as well as after 15 days, also there was a highly strong positive link between it and functional outcome as assessed by mRS after 15 days follow up. Moreover , a significant negative correlation between serum level of MMP-9 and GCS at admission and BI after 15 days was found in our study.MMP-9 showed highly significant positive correlation with brain infarction size (table 3).Table (4) showed that the best cutoff of MMP-9 predicting large size brain infarction was ≥1042 ng/ml with area under curve 0.764, sensitivity 81%, specificity 63.6%, positive predictive value 58.6%, negative predictive value 84%, and overall accuracy 70.4% ($p<0.001$) (figure 1). The best cutoff level of MMP-9 in prediction of severe stroke was ≥1091ng/ml with area under curve 0.878, sensitivity 84%, specificity 63.6%, positive predictive value 75%, negative predictive value 84.6%, and overall accuracy 79.6% ($p<0.001$) (figure 2). serum level of MMP-9 ≥972.5 ng/ml was significant in detection of poor outcome after 15 days with area under curve 0.929, sensitivity 90%, specificity 85.7%, positive predictive value 94.7%, negative predictive value 75%, and overall accuracy 88.9% ($p<0.001$)(figure3) Among factors significantly correlated with baseline NIHSS, MMP-9 (unstandardized $\beta=0.01$, $p=0.001$), size of brain infarct (unstandardized $\beta=1.688$, $p=0.002$) and BI (unstandardized $\beta=-0.085$, $p<0.001$) significantly independently associated with baseline NIHSS and stroke severity among studied patients. Also, mRS only significantly independently associated with baseline NIHSS among studied patients (unstandardized $\beta=0.158$, $p=0.001$), (table 5).

Table (1): Demographic, clinical characteristics and serum MMP-9 level of the studied ischemic stroke patients

	N=54	%
Sex:		
Female	31	57.4%
Male	23	42.6%
Age (year):		

	N=54	%
Mean ± SD Range	64.2 ± 7.96 50 – 85	
Diabetes	31	57.4%
Hypertension SBP in mmHgAverage SD DBP in mmHgAverage SD	43 165.19 ± 25.68 95.91 ± 12.2	79.6%
Smoker	20	37%
Cardiac	22	40.7%
Obesity	25	46.3%
Dyslipidemia	19	35.2%
Migraine	10	18.5%
Oral contraceptive pills	(12/31)	38.7%
MMP-9 (ng/ml) Mean ± SD	1085.93 ± 248.29	
Range	485 – 1544	

BP: Blood pressure SBP: Systolic blood pressure DBP: Diastolic blood pressure
MMP-9:Matrix Metalloproteinase-9

Table (2): stroke severity as determined by the NIHSS and GCS at admission and after 15 days of follow up

	Baseline	After 15 days	T	p
	Mean ± SD	**Mean ± SD**		
NIHSS	13.43±5.46	9.96 ± 4.95	9.046	<0.001**
GCS	11.96 ± 2.46	13.69 ± 1.4	-6.777	<0.001**

The paired sample t test yielded a statistically significant result of **p0.001.
GCS :Glasgow Coma Scale NIHSS:the National Institutes of Health Stroke Scale

Table (3): correlation between serum level of MMP-9, NIHSS, GCS, BI, mRS and infarction size among studied patients

	r	P
NIHSS (at admission)	0.783	<0.001**
NIHSS after 15 days	0.565	<0.001**
GCS (at admission)	-0.872	<0.001**
GCS after 15 days	-0.565	<0.001**
mRS	0.631	<0.001**
BI	-0.45	<0.001**
Size of brain infarction	0.609	<0.001**

Statistics show that r Pearson correlation coefficient **p0.001 is extremely significant.
GCS:Glasgow Coma Scale NIHSS: the National Institutes of Health Stroke Scale MMP-9: matrix metalloproteinase-9 BI:Barthel index MRS: modified Rankin scale

Table (4): The cutoff point of serum level of MMP-9 in detection of large infarction, stroke severity and poor outcome the studied patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
Large infarction							
≥1042	0.764	81%	63.6%	58.6%	84%	70.4%	0.001**
Stroke severity							
≥1091	0.878	84%	75.9%	75%	84.6%	79.6%	0.001**
Poor outcome							
≥972.5	0.929	90%	85.7%	94.7%	75%	88.9%	<0.001**

**p≤0.001 is statistically highly significant Area Under Curve (AUC)
PPV:Positive predictive value NPP: negative predictive power

Table (5): variables predicted using multivariate logistic regression analysis of stroke deterioration and poor outcome among studied patients

	Unreliable Coefficients		Normative Coefficients	t	p	95.0% Confidence Interval	
	β	Std. Error	Beta			Lower	Upper
(Constant)	4.654	2.557		1.820	0.075	-0.482	9.790
MMP-9	0.010	0.002	0.468	5.807	0.001**	0.007	0.014
BI	-0.085	0.018	-0.351	-4.686	0.001**	-0.121	-0.048
Size of infarct	1.688	0.530	0.265	3.184	0.002*	0.623	2.753
NIHSS							
(Constant)	1.216	0.240		5.059	<0.001**	0.734	1.699
NIHSS	0.158	0.017	0.796	9.494	<0.001**	0.124	0.191

A statistically significant result is one with a p-value of 0.05 or above.
NIHSS: National Institute of Health Stroke Scale MMP-9 Matrix Metalloproteinase-9
Index

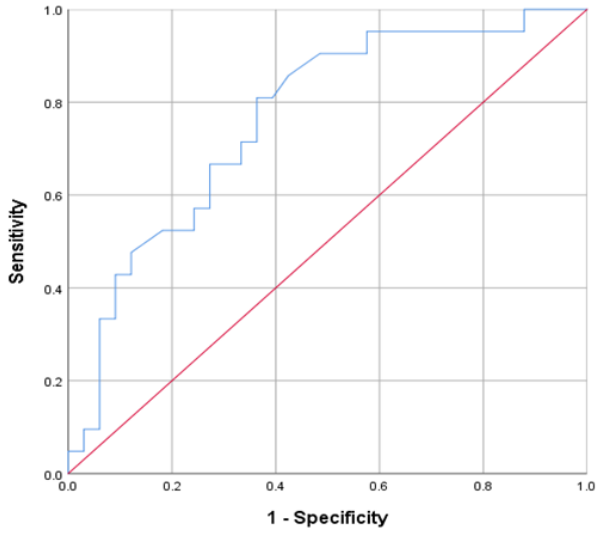

Figure (1): ROC curve displaying the efficiency of MMP-9 in detection of large infarction among the patients under study

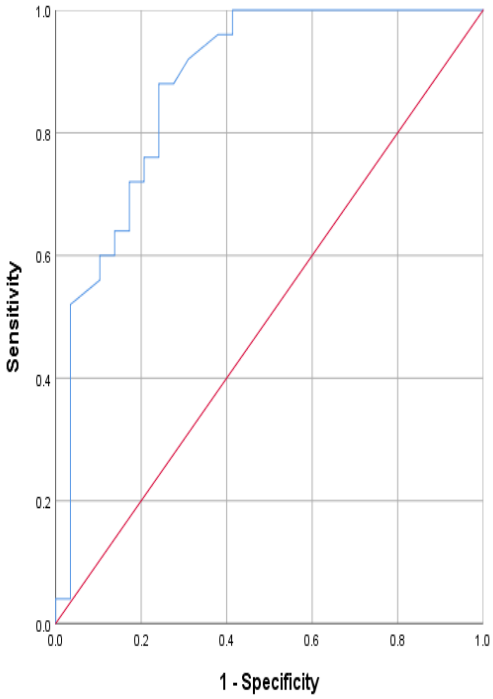

Figure (2): ROC curve displaying the efficiency of MMP-9 in detection of severe stroke baseline among the patients under study

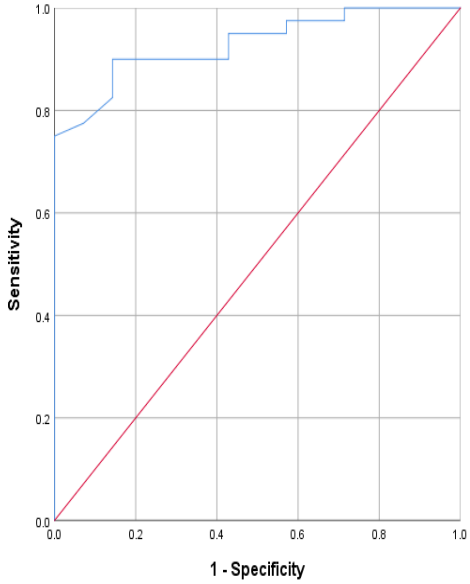

Figure (3):ROC curve displaying the efficiency of MMP-9 in detection of poor outcome among the patients under study

DISCUSSION

This cohort study was done in Emergency Unit and Stroke Unit of Neurology Department, Zagazig University Hospitals. Fifty -four individuals who had acute ischemic stroke for the first time participated in this research. We noticed that age ranged from 50 to 85 years with mean 64.2 years. This is consistent with **[12]** who quoted mean ages between 31 and 88 years. Regarding sex distribution among studied patients, we noticed that 57.4% of recruited patients in the current study were females and 42.6% were males, a finding which was in accordance to Weimar et al. **[13]** who found in their study that 846 (43.1%) were women. On the other hand, Barrett et al. **[14]** frequently noticed that males experience incidence rates that are 25% to 30% higher.

In agreement to this finding, according to the American Rothwell Rochester research

done in the United States, female strokes were 16255 compared to 14149 male strokes, which suggests that women outweigh men by a ratio of 1.15. Women are commonly affected by strokes than males in their parents. The effects of oestrogen on cerebral circulation may provide another explanation **[15].**

In our study, mean MMP-9 was 1085.93 ng/ml with a range from 485 to 1544 ng/ml. Zhong et al**. [16]** investigated the relationship between prognosis and serum MMP-9 levels in subjects with an acute ischemic stroke. Typical serum MMP-9 levels concentration was 671.8 ng/mL (interquartile range 414.7–1,025.8 ng/mL). Our study finding additionally concurred with that of Abdelnaseer et al. **[17]** who stated that patients' mean serum MMP-9 levels were significantly higher than controls'.

In the present study, on assessing stroke severity, we found that the patients had statistically significant higher mean scores of GCS and NIHSS on admission than after 15 days of follow up denoting improvement of stroke severity. Mean baseline patients' NIHSS score was 13.43 ± 5.46 and it was 9.96 ± 4.95 after 15 days, with a statistically significant decrease in NIHSS after 15 days as compared to baseline value.

Results by Abdelnaseer et al**. [17]** who investigated the relationship between the blood level of matrix metalloproteinase-9 (MMP-9) within 24 hours of acute ischemic stroke onset and clinical severity and discovered that patients' NIHSS score ranged from 4 to 20. In addition, Poudel et al. [**18]** demonstrated that NIHSS rating was connected to the three-month prognosis in stroke patients. In agreement to these results, Acute stroke patients' seven-day mortality in ICUs was predicted by the NIHSS score upon admission in a research conducted in Nepal, but long-term determinants of outcomes were not examined. Regarding ICU admission, the NIHSS score was not predictive **[19**]. Additionally, a statistically significant positive correlation between serum levels of MMP-9 and the severity of stroke was also revealed by the current study's findings assessed by NIHSS at admission and after 15 days. Also, MMP-9 had a strong positive correlation that was statistically significant with functional outcome as assessed by mRS after 15 days follow up. But, the blood level of MMP-9 had a statistically significant negative correlation with GCS at admission and following 15 days, also, a significant negative statistical correlation between BI and MMP-9 was documented by the findings of this study. These findings backed up MMP-9's role as a biomarker that independently predicts neurological impairment in the acute stage and also as a prognostic factor of short-term outcome.

Our findings were in accordance to study of Ning et al**. [20]** who reported that MMP-9 levels measured during the hyperacute phase were correlated to mRS at 3 months among 52 consecutive ischemic stroke patients. Abdelnaseer and colleagues **[17]** postulated that patients with normal levels of MMP-9 had mean NIHSSs that were lower than those with elevated MMP-9 serum levels. The first stroke severity as determined by the NIHSS score and the blood level of MMP-9 showed a statistically significant positive connection. However, there was no discernible connection between the patients' ages and their serum MMP-9 levels.

Data obtained by this research illustrated the most accurate MMP-9 cut off level in the prediction of large size infarction, that was ≥ 1042 Also, the best cut off of MMP-9 in diagnosing severe stroke was ≥ 1091ng/ml. Zhong et al. **[16]** obtained a good MMP-9 cut point level (812.2 ng/mL) from the curve of the receiver operating characteristic. In the current study, it was found also that the best cutoff of MMP-9 in prediction of severe stroke after 15 days is ≥972.5 ng/ml with area under curve of 0.929, sensitivity of 90%, specificity of 85.7%, positive predictive value of 94.7%, negative predictive value of 75%, and overall accuracy of 88.9% ($p<0.001$).

On the multivariate regression model, it was recorded that MMP-9, size of infarct, BI and mRS were among factors that significantly and independently correlated with baseline NIHSS score among ischemic stroke subjects who were enrolled in this study.

Geng et al**. [21]** demonstrated the outcomes of the multiple logistic regression analysis for identifying the determinants of early neurological deterioration (END). Diabetes and NIHSS score on admission were

significantly independent END predictors. END was a significant predictor of poor functional result and was linked to mortality over the follow-up period. Poor functional outcomes were also linked to advanced age, a high BMI, coronary heart disease, and elevated CRP levels. Zhong et al. **[16]** showed a linear relationship between MMP-9 levels and the overall outcome and major disability at 3 months.

CONCLUSION

The current study's findings concluded that blood MMP-9 levels were elevated on the first day following an acute ischemic stroke, hence the blood level of MMP-9 on the first day following an acute ischemic stroke is positively correlated with initial stroke severity. So, we can conclude that MMP-9 serum level may have a predictive value as a biomarker for prediction of initial stroke severity and short-term prognosis in individuals with ischemic stroke as well. Further research on this subject is warranted in order to decrease the load of unfavorable results and also studies of the time-dependent effect of MMP-9 on prognosis after stroke are recommended.

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