ISSN NO: 2770-2936
August 2025

Pla2eg2 In Predicting The Outcomes Of The Early Recovery Period Of Stroke

Gazieva Sh.R., Rakhimbayeva G.S.
Tashkent State Medical University

Abstract: PLA2G2E plays a pro-survival and pro-reparative role in periinfarction neurons, contributing to recovery after stroke. PLA2G2E levels below 0.580 units are associated with an increased risk of mortality. Exceeding this threshold significantly improves survival and functional outcome (according to the Rankin and Bartel scales). Measuring PLA2G2E levels on the first day after a stroke can help assess the prognosis and adjust treatment to improve survival and restore function.
Key words: PADI4, ischemic stroke, PLA2G2E, DGLA

Introduction. Stroke is the leading cause of disability and the second most common cause of death in the world, and its frequency is increasing due to an aging population. Early diagnosis is crucial for timely medical intervention. Biomarkers serve as objective indicators for predicting outcomes, monitoring treatment responses, and evaluating prognosis. Blood biomarkers are readily available and provide insight into the pathophysiological processes underlying stroke.

Biomarker measurement time is especially important in the early stages of stroke, when rapid decision-making is necessary, and this requires systematic investigation. Although many molecules have been proposed as biomarkers of stroke in recent years, none of them has yet been integrated into everyday clinical practice. Biomarkers of stroke offer great prospects for improved diagnosis, risk stratification, and personalized treatment strategies. However, well-thought-out research and rigorous verification are needed to bridge the gap between research results and clinical implementation. The integration of biomarkers with existing diagnostic tools can revolutionize stroke treatment and improve patient outcomes. Continued research on blood biomarkers and their clinical usefulness remains a prerequisite for improving stroke treatment.

Biomarkers can be defined as indicators that objectively assess normal and pathological processes, evaluate therapeutic response, and predict outcomes [1]. Biomarkers can be molecules found in body fluids such as cerebrospinal fluid or blood, or physical measurements of tissues. Proteins, metabolites, lipids, and RNA are examples of molecular biomarkers that can be used individually or in combination as panels, scores, or indexes. Several biomarkers are already used in everyday clinical decision-making.; For example, troponin T helps to diagnose myocardial infarction, and D-dimer is used for pulmonary embolism, plasma creatinine for kidney function, and C-reactive protein for infections [2].

After a stroke, a number of pathophysiological events occur that gradually cause damage to neurons and eventually lead to cell death if left untreated [3]. This process follows a time-dependent pattern, with each stage characterized by unique biochemical changes and the release of specific biomarkers that can aid in early diagnosis. The neurovascular unit, as a multicellular structure, is a potential source of biomarkers of cerebrovascular diseases.

Just as in other painful conditions, the body signals the nature of the processes taking place in it through a number of biomarkers. One of the potential such indicators is considered to be the level of PLA2G2E (phospholipase A2 of group IIE, an enzyme) in blood plasma. The role of this signaling protein has been repeatedly discussed and confirmed in a number of scientific papers [4].

Despite the fact that the brain is capable of some regeneration in case of damage, its capabilities in this regard are limited. The causes and details of the self-healing processes occurring in the brain are not yet well understood. A study by Nakamura Akari et al. (2023) found that secreted phospholipase PLA2G2E, produced by neurons near the lesion, creates digomo-γ-linolenic acid (DGLA), which plays a key role in activating cerebral self-healing after ischemic stroke. A decrease in PLA2G2E levels leads to a decrease in the expression of peptidyl arginine deiminase 4 (PADI4), an important transcription regulator in peri-infarct neurons. Single-cell RNA sequencing (scRNA-seq) and epigenetic analysis have shown that neural PADI4 is able to activate genes involved in recovery from ischemic stroke through histone citrullination. Among the DGLA metabolites, 15-hydroxy-eicosatrienoic acid (15-HETrE) was identified as a substance that stimulates PADI4 activity

ISSN NO: 2770-2936
August 2025

in neurons near the lesion site. The introduction of 15-HETrE into the body improved functional recovery after ischemic stroke. The data obtained demonstrate the potential of using stimulation of the brain's natural self-healing ability caused by certain fats to accelerate tissue regeneration after brain damage.

The main functions of a protein known as PLA2GE2 (phospholipase A2 of group IIE, an enzyme) are an indirect increase in DGLA and an effect on functional recovery. PLA2GE2 deficiency leads to more inflammation, decreased levels of a protein called peptidylargine deiminase 4 (PADI4) and expression of factors that stimulate neuronal repair, and greater tissue loss. PLA2G2E is an enzyme that is released outside of cells and acts as; It is believed that PLA2G2E is released from nerve cells around the site of cerebral infarction and produces unsaturated fatty acids from the remains of cell membranes of dead nerve cells [4].

Currently, the main areas of study of PLA2GE2 are cancers of the gastrointestinal tract in humans, in which it was found that PLA2G2A expression significantly correlated with patient survival [5]. Currently, there is very little data in the scientific literature on the study of the role of PLA2G2A in patients with ischemic stroke, which served as the basis for conducting and defining the goals of this study.

Materials. The study examined 138 patients admitted to the basic hospital of the Department of Neurology of the Tashkent Medical Academy and the 4th City Clinical Hospital of Tashkent. The conditions for participation in the study were: diagnosed ischemic stroke, confirmed by neuroimaging methods, the age of patients aged 18 years and above, admission to the clinic in the first 24 hours after the onset of the disease, the absence of exacerbations of chronic or acute diseases of internal organs, as well as oncological diagnoses.

A total of 138 patients participated in the clinical trial. The average age of the patients was 64.7±0.92 years. The patients were divided into 2 groups, with low (GLL PLA2G2E) and high (GHL PLA2G2E) PLA2G2E levels (table 1).

Table 1.

Characteristics of the clinical research object

	Characteristics of the groups		Women		Men	
			n	Age M_{cp}	n	Age M_{cp}
1	ГВУ PLA2G2E	n = 70	23	64,1±1,95	47	64,5±1,42
2	ГНУ PLA2G2E	n = 68	26	63,4÷2,08	42	65,2±1,83

When considering the possibility of thrombolysis, additional criteria for selecting patients were applied, corresponding to the current recommendations for thrombolysis.The patients were prescribed standardized basic treatment, and if necessary, thrombolytic and antithrombotic drugs were used [6].

In these groups, both clinical neurological and anamnestic examinations were performed in accordance with the standards of neurological examination [7,8]. The diagnosis of AI was established according to the criteria of ICD 10, the classification of O.S. Levin (2006), after collecting anamnesis, a thorough clinical and neurological examination, a study of the functions of the cognitive sphere, and magnetic resonance imaging (MRI). Nonparametric methods were used to process the results of laboratory tests and obtain clinical statistics. The degree of axiomaticity of P was 0.05. A clinical and neuropsychological assessment of patients was performed using special Rankin scales, Rivermead, MoCA (The Montreal Cognitive Assessment), NIHHS (National Institutes of Health Stroke Scale), Barthel index (Table 2). Neuroimaging research methods (MRI) were performed.

Таблица 2.

Scale indicators in the examined patients at the beginning of treatment (score) (M±m)

Groups	NIHSS	Rankin	Rivermead	MOCA	Barthel
GHL PLA2G2E (n=70)	9,70±0,32	3,59±0,09	5,11±0,45	21,1±0,31	64,8±0,81
GLL PLA2G2E (n=68)	9,91±0,44	3,72±0,07	4,42±0,51	19,4±0,22	51,9±0,92

ISSN NO: 2770-2936
August 2025

3-rd group (healthy) (n=30)	1,12±0,18	0,52±0,05	14,8±0,11	26,8±0,18	99,8±0,34

PLA2G2E (phospholipase A2 Group IIE) was determined using a Sigma-Aldrich kit using an anti-PLA2G2E antibody obtained in purified immunoglobulin. Antibodies for detection in the sandwich ELISA kit-ELISA analysis. The immunogen in this case is PLA2G2E, a full-sized human protein. In healthy patients, PLA2G2E levels ranged from 0.634 units to 0.952 units.

The data obtained during the clinical trial was analyzed using the STATISTICA program for Windows 6.0.

Results and discussion. During the first month of follow—up of patients with ischemic stroke, death was observed in 16.6% of cases (in 23 people), with the most common death occurring on the tenth day of the disease (interquartile range: 4.9-16), mainly due to cerebral edema. Fatal outcomes were observed in the group with low PLA2G2E values. According to the results of the Cox regression analysis conducted in stages, statistically significant negative effects of low PLA2G2E levels on the probability of death were observed (B = 0.324). The odds ratio (OR) was 0.72.

According to the results of the study, a decrease in PLA2G2E levels by one unit was accompanied by a 0.72-fold increase in the probability of death. Kaplan—Meyer curves demonstrated a higher risk of death at low levels of PLA2G2E compared with the probability of survival. The Kaplan—Meyer analysis revealed a threshold PLA2G2E level associated with an increased mortality risk of 0.580±0.04 (93%) units, which is confirmed by the coordinates on the characteristic curve.

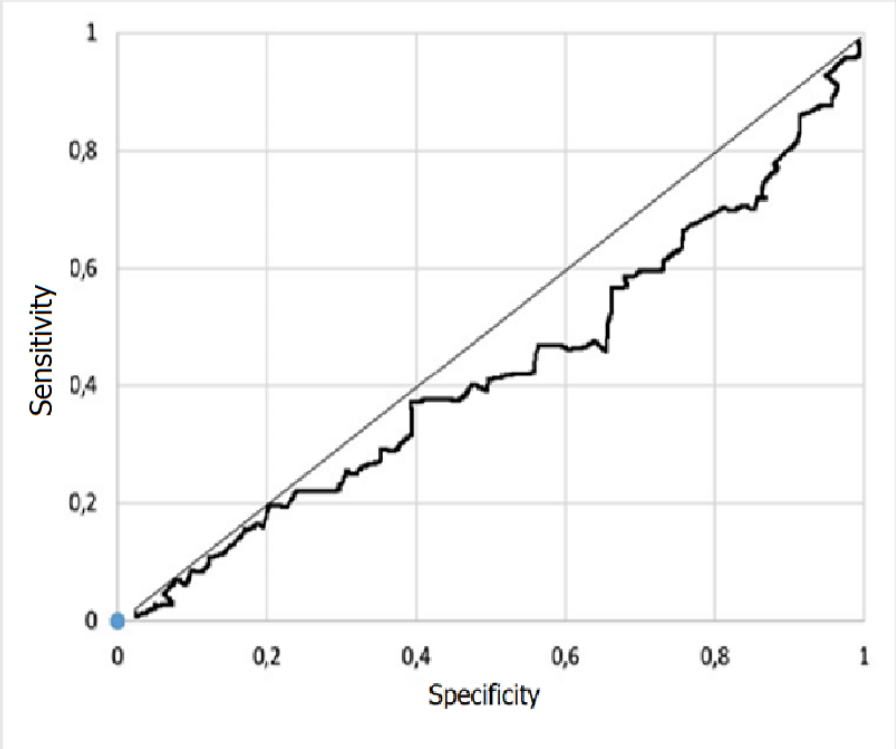

Fig.1 Relationship between PLA2G2E level and probability of death

The accuracy of the PLA2G2E test at a level above 0.580 units for predicting death was 48.3% (95% confidence interval: 37.5—51.8%), and at a level below – 74.8% (95% confidence interval: 65.7—81.1%). An analysis of the operating curve reflecting the probability of death showed that PLA2G2E was statistically significantly associated not with the outcome towards death, but with the opposite – with survival, since the curve was located below the diagonal line (see Fig.1). Therefore, an increase in PLA2G2E concentration above 0.580 U correlates with an increased chance of survival in patients who have suffered an ischemic stroke.

A sequential logistic regression analysis was performed to study the effect of PLA2G2E on improving functional status, measured on the Rankine scale. The odds ratio (OR) was 1.54, which suggests that an increase in PLA2G2E concentration per unit is associated with a 1.54-fold increase in the probability of a favorable

ISSN NO: 2770-2936
August 2025

outcome on the Rankine scale. The analysis based on the Kaplan-Meyer method revealed a threshold level of PLA2G2E, significant for predicting improvement in the functional state on the Rankine scale, which was confirmed by analyzing the points of the curve – 0.580 units. (95%). The prognostic value of exceeding this threshold (PLA2G2E >0.580 units) for a favorable outcome was 69.1%, while for an unfavorable outcome it was 52.8%. The curve reflecting the prognosis of the severity of the condition confirmed the statistical significance of PLA2G2E in predicting improvement in functional status on the Rankine scale. The area under the curve was 0.73.

The use of logistic regression, the Kaplan—Meyer method, as well as visualization of the relationships with the Bartel index and the MOSA questionnaire revealed a correspondence with the data obtained in the PLA2G2E assessment using the Rankine scale. In this regard, the same PLA2G2E threshold level as for the Rankine scale was used to predict a favorable functional outcome according to the Barthel index and the MOSS scale: 0.580 units. This threshold turned out to be more informative when assessing the probability of a good functional recovery using the Barthel index and the MOSS scale than when using the Rankin scale. The relative risk (OR) was 91.1, which means that an increase in PLA2G2E by one is associated with a 1.5-fold increase in the probability of achieving a good functional result according to the Barthel index and the MOSS scale. The prognostic value of a positive test (PLA2G2E > 0.580 units) for functional recovery according to the Barthel index and the MOSS scale was 78.8%, and a negative test was 52.9%.

Conclusion. In conclusion, comparing the data obtained during the study with the already known information about the neuroprotective function of PLA2G2E, we can conclude that this protein plays a pro-survival and pro-reparative role in periinfarction neurons to improve recovery after stroke. A PLA2G2E value below 0.580 units is associated with an increased risk of mortality. The PLA2G2E level exceeding the specified limit significantly improves the chances of survival, and its further increase, above 0.580 units, correlates with the subsequent favorable functional outcome, assessed on the Rankine and Bartel scales. Therefore, measuring PLA2G2E levels on the first day (it has a neuroprotective function from day 1 to day 4) [4] in the body after the development of an ischemic stroke can help assess the likely outcome of the disease and suggest how to change supportive treatment to increase the chances of survival and restoration of lost functions.

References

1.Ahmad, A.; Imran, M.; Ahsan, H. Biomarkers as biomedical bioindicators: Approaches and techniques for the detection, analysis,and validation of novel biomarkers of diseases. Pharmaceutics 2023, 15, 1630. [CrossRef].

2.Dagonnier, M.; Donnan, G.A.; Davis, S.M.; Dewey, H.M.; Howells, D.W. Acute Stroke Biomarkers: Are we there yet? Front. Neurol.2021, 12, 619721. [CrossRef].

3.Kamtchum-Tatuene, J.; Jickling, G.C. Blood biomarkers for stroke diagnosis and management. NeuroMolecular Med. 2019, 21, 344–368. [CrossRef] [PubMed].

4.Nakamura Akari et al. PLA2G2E-mediated lipid metabolism triggers brain-autonomous neural repair after ischemic stroke. Neuron. 2023; Volume 111, issue 19: P2995-3010 DOI:https://doi.org/10.1016/j.neuron.2023.06.024 S0896-6273(23)00483-X.

5.Wang X, Huang CJ, Yu GZ, Wang JJ, Wang R, Li YM, Wu Q. Expression of group IIA phospholipase A2 is an independent predictor of favorable outcome for patients with gastric cancer. Hum Pathol. 2013 Oct;44(10):2020-7. doi: 10.1016/j.humpath.2013.01.027. Epub 2013 May 10. PMID: 23664539.

ISSN NO: 2770-2936
August 2025

6.Skvortsova V.I., ed. Thrombolytic therapy in patients with ischemic stroke : a methodological guide. Moscow; 2010. (in Russian) 11. Hacke W. ECASS Investigators. Thrombolysis with alteplase 3 to 4,5 hours after acute ischemic stroke. N. Engl. J. Med. 2008; 13: 1317—29.

7. Mikhailenko, A.A. Clinical practice in neurology., Publisher: St. Petersburg: Folio, 480 pages; 2001. ISBN: 5-93929-018-3

8. Skoromets, A. N. Topical diagnostics of diseases of the nervous system: guidance for doctors / A. A. Skoromets, A. P. Skoromets, T. A. Skoromets. – 8th ed., reprint. and add. – St. Petersburg : Polytechnic, 2012. - 623 p.