

Importance of Serum Biomarkers for Early Diagnosis of Acute Ischemic Stroke: What's New

© Neeraj Kumar

Department of Anaesthesiology, All India Institute of Medical Sciences Patna, Bihar, India

Keywords: Acute ischemic stroke, biomarkers, diagnosis, management

Ischemic and hemorrhagic strokes are two important components of strokes and globally these strokes are the leading cause of mortality and long-term disability (1). Acute ischemic strokes (AIS) have a greater incidence than hemorrhagic strokes and they present with sudden onset of acute neurological deterioration. The outcome of these stroke patients depends on early and prompt diagnosis at the time of admission and quick restoration of normal cerebral blood flow required (2). Globally more than 12.2 million new strokes each year and one in four people over age 25 will have a stroke in their lifetime. Over 62% of all incident strokes are ischaemic strokes (3).

For predicting neurological deficits and mortality, and for making earlier diagnoses of AIS several studies have been conducted so far. Several prognostic markers like glucose, iron, ferritin, homocysteine, insulin, P-selectin, matrix metalloproteinase-9 (MMP-9), high-density lipoprotein-cholesterol, platelets, C-reactive protein, glial fibrillary acidic protein (GFAP), tumor necrosis factor-alpha, interleukin-6, and proenkephalin-A have been recently investigated and they have added value in rapidly diagnosing and predicting mortality and prognosis in AIS (4-9). However, for a better practical perspective, early, rapid, and cost-effective diagnostic techniques for the management of AIS are still awaited.

An ideal stroke biomarker(s) should be able, with high specificity and sensitivity, to differentiate between subtypes of ischemic and hemorrhagic stroke. They should not only predict stroke prognosis but also facilitate therapeutic stratification and therapeutic monitoring.

Non-contrast computed tomography (NCCT) brain is the earlier investigation for most suspected stroke patients. The clinicians become uncertain about the initiation of thrombolysis or using stroke prevention when NCCT brain is normal. So, if a patient has clinical symptoms of AIS in such cases blood biomarker may be an important useful test. AIS is an inflammatory process following endothelial dysfunction involving large and medium-sized arteries, monocyte migration, and the release of cytokines and growth factors that may lead to a rise in various other specific proteins. The role of neuroglial inflammation in the infarct core and ischemic penumbra has been better understood using inflammatory biomarkers. Few proteins are found mainly in the nervous system: B-type neurotrophic growth factor, S100-beta, myelin basic protein (MBP), neurone-specific enolase (NSE), and visin-like protein; others indicate endothelial processes: MMP-9, thrombomodulin, vascular cell adhesion molecule (VCAM), and Von Willebrand Factor (vWF) (10).

Few published literature like Zhou et al. (11) reported that measuring S100B (glial protein, highly specific to nervous tissue) within the first 6 h of stroke helped differentiate ischemic stroke from intracranial haemorrhage (ICH) (sensitivity of 95.7%, specificity of 70.4%, using a cut-off of 67 pg/mL).

Xiong et al. (12) showed that the GFAP (glial protein specific to astrocyte) concentration in blood collected within 2-6 h after symptom onset was significantly higher in ICH (n=43) than IS (n=65) patients, with 86 and 76.9% sensitivity and specificity of, respectively, using a cut-off point of 0.7 ng/mL.



Corresponding Author: Neeraj Kumar MBBS (Hons), MD, Assoc. Prof., Department of Anaesthesiology, All India Institute of Medical Sciences Patna, Bihar, India
Phone: +91 8210104972 **E-mail:** drneerajk@aiimspatna.org **ORCID ID:** orcid.org/0000-0002-9161-7000

Cite this article as: Kumar N. xxx Eurasian J Emerg Med. Eurasian J Emerg Med. Eurasian J Emerg Med. 2023;22(3): 133-4.



©Copyright 2023 The Emergency Physicians Association of Turkey / Eurasian Journal of Emergency Medicine published by Galenos Publishing House.
Licenced by Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND) 4.0 International License.

Received: 20.08.2023
Accepted: 29.08.2023

Lu et al. (13) assessed serum NSE levels prospectively within 4.5 h of AIS symptom onset in rt-PA treated patients (n=67) correlates with the National Institutes of Health Stroke Scale (NIHSS) at 24 h (R=0.342), and lower serum NSE levels and NIHSS scores were detected in patients with favourable neurological outcomes after 90 days.

Ramos-Fernandez et al. (14) suggested that the rise of MMP-9 is not specific to ischemic stroke, moreover, its concentration is reported to peak at 24 hours post-stroke, which is too late for making decisions about thrombolysis.

Oraby and Rabie (15) concluded that thioredoxin is a marker of oxidative stress and has been used as a new diagnostic and prognostic blood biomarker for AIS. Using the receiver operator curve, the best cut-off limit of thioredoxin levels early after admission (in the first 24 hours of stroke) in predicting poor outcome was 21.89 ng/mL (88% sensitivity and 64% specificity).

However, andropin (a peptide hormone) improves vascular endothelial cell function by regulating endothelial nitric oxide synthase and shows anti-inflammatory properties by increasing the proliferation of endothelial cells and capillary-like structure and further aids in the diagnosis of AIS in emergency settings as an independent biomarker. In this regard, the prospective clinical study entitled "Importance of Serum Andropin Levels in Ischemic Stroke" published in this issue of the Eurasian Journal of Emergency Medicine is interesting and provides an additional diagnostic value of AIS based on significantly high serum Andropin level than those of control group (16). Nearly all of the serum biomarkers research that has been reported thus far in the field of stroke is exploratory in nature. A consortium has been already created (Human Brain Proteome Project) to facilitate the identification of potential brain markers with proteomic techniques (17). A well-designed trial is required to delineate the associations between biomarkers and clinical outcomes is further required.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018;49:46-110.
3. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Available from: https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf
4. Vila N, Castillo J, Dávalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke*. 2000;31:2325-9.
5. Hasan N, McColgan P, Bentley P, Edwards RJ, Sharma P. Towards the identification of blood biomarkers for acute stroke in humans: a comprehensive systematic review. *Br J Clin Pharmacol*. 2012;74:230-40.
6. Schiff L, Hadker N, Weiser S, Rausch C. A literature review of the feasibility of glial fibrillary acidic protein as a biomarker for stroke and traumatic brain injury. *Mol Diagn Ther*. 2012;16:79-92.
7. Lehmann MF, Kallaur AP, Oliveira SR, Alfieri DF, Delongui F, de Sousa Parreira J, et al. Inflammatory and metabolic markers and short-time outcome in patients with acute ischemic stroke in relation to TOAST subtypes. *Metab Brain Dis*. 2015;30:1417-28.
8. Doehner W, von Haehling S, Suhr J, Ebner N, Schuster A, Nagel E, et al. Elevated plasma levels of neuro peptide proenkephalin predict mortality and functional outcome in ischemic stroke. *J Am Coll Cardiol*. 2012;60:346-54.
9. Basic Kes V, Simundic AM, Nikolac N, Topic E, Demarin V. Pro-inflammatory and anti-inflammatory cytokines in acute ischemic stroke and their relation to early neurological deficit and stroke outcome. *Clin Biochem*. 2008;41:1330-4.
10. Whiteley W, Tseng MC, Sandercock P. Blood biomarkers in the diagnosis of ischemic stroke: a systematic review. *Stroke*. 2008;39:2902-9.
11. Zhou S, Bao J, Wang Y, Pan S. S100β as a biomarker for differential diagnosis of intracerebral hemorrhage and ischemic stroke. *Neurol Res*. 2016;38:327-32.
12. Xiong L, Yang Y, Zhang M, Xu W. The use of serum glial fibrillary acidic protein test as a promising tool for intracerebral hemorrhage diagnosis in Chinese patients and prediction of the short-term functional outcomes. *Neurol Sci*. 2015;36:2081-7.
13. Lu K, Xu X, Cui S, Wang F, Zhang B, Zhao Y. Serum neuron specific enolase level as a predictor of prognosis in acute ischemic stroke patients after intravenous thrombolysis. *J Neurol Sci*. 2015;359:202-6.
14. Ramos-Fernandez M, Bellolio MF, Stead LG. Matrix metalloproteinase-9 as a marker for acute ischemic stroke: a systematic review. *J Stroke Cerebrovasc Dis*. 2011;20:47-54.
15. Oraby MI, Rabie RA. Blood biomarkers for stroke: the role of thioredoxin in diagnosis and prognosis of acute ischemic stroke. *Egypt J Neurol Psychiatry Neurosurg*. 2020;56:2-8.
16. Laterza OF, Modur VR, Crimmins DL, Olander JV, Landt Y, Lee JM, Ladenson JH. Identification of novel brain biomarkers. *Clin Chem*. 2006;52:1713-21.
17. Tekin E, Koçak MN, Bayraktar M, Özlü İ, Çelik M, Kurt E, Halıcı Z. Importance of Serum Andropin Levels in Ischemic Stroke: A Prospective Clinical Study. *Eurasian J Emerg Med*. [Epub Ahead of Print]. Doi: 10.4274/eajem.galenos.2023.03780