



# **A Study Protocol for Estimating the Association of De Ritis ratio (AST/ALT) with Outcomes in Patients of Acute Ischemic Stroke**

**Shubham Nimkar <sup>a\*≡</sup>, Anuj Varma <sup>a⊖</sup>, Sourya Acharya <sup>a#</sup>, Sunil Kumar <sup>a#</sup>,  
A. K. Wanjari <sup>a#</sup> and Shilpa Bawankule <sup>a#</sup>**

<sup>a</sup> *Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.*

## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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**Study Protocol**

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## **ABSTRACT**

**Background:** One of the clinical endpoints of atherosclerosis is stroke, the most prominent clinical manifestation of cerebrovascular disease. It is a cerebral blood vessel disease that nourishes the brain. A global health concern is stroke. It is the second most prevalent cause of death worldwide and the fourth leading cause of disability. The underlying pathophysiology in most ischemic strokes is atherosclerosis. Few studies have shown that high AST/ALT ratio was independently correlated with the increased danger of complication and death in cerebrovascular event patients. This research aims to assess the correlation of De Ritis ratio in cases of acute ischaemic stroke at admission and their prognosis at 3 months.

**Methodology:** This will be an observational cross-sectional study. About 65 patients with signs suggestive of acute ischemic stroke will be examined. A comprehensive laboratory examination will be carried out. For confirmation of the diagnosis, all patients will undergo CT SCAN or MRI assessment. The primary results of stroke severity on admission will be obtained according to the NIHSS scale. The ranking for NIHSS would be dichotomized to less than 5 and more than 5. For all

<sup>≡</sup> Post Graduate Student;

<sup>⊖</sup> Associate Professor;

<sup>#</sup> Professor;

\*Corresponding author: E-mail: shubhamnimkar7@gmail.com;

cases diagnosed with acute ischemic stroke, AST/ALT RATIO will be computed. Data will be analysed with relevant statistical tests.

**Results Expected:** We expect a significant correlation between serum de-Ritis ratio and prognosis of acute ischaemic stroke.

*Keywords: AST/ALT ratio; Acute ischaemic stroke; alanine transaminase (ALT); modified rankin scale; prognosis.*

## 1. INTRODUCTION

One of the clinical endpoints of atherosclerosis is stroke, the most prominent clinical manifestation of cerebrovascular disease. It is a cerebral blood vessel disease that nourishes the brain. The World Health Organization (WHO) describes stroke as an occurrence that causes blood flow to the brain to be disrupted, usually due to blockage of the blood vessels or collapse of the blood vessels. A global health concern is stroke. It is the second most prevalent cause of death worldwide and the fourth leading cause of disability. The underlying pathophysiology in most ischemic strokes is atherosclerosis. Few studies have shown that high AST/ALT ratio was independently correlated with the increased danger of complication and death in cerebrovascular event patients. The study conducted in this research is prospective type which will assess the 3 monthly outcome in patients of cerebrovascular event and will correlate them with the AST/ALT done at the time of admission. With higher mortality rates, stroke is a severe disease. It is ranked as the world's 2nd and 3rd deadliest disease and disability.[1] Predicting the prognostic outcome of stroke patients in the early stages is helpful for obtaining adequate care from doctors, having good results on management and enhancing total coverup. extra study on the outcome of stroke is immediately required.

A positive association of two blood enzymes, aspartate transaminase (AST) and alanine transaminase (ALT), with a full result after acute ischaemic stroke has been documented (AIS). [2,3] The physiological impact of AST and ALT on the reduction of blood glutamate levels may be the reason for this. It was possible to observe neuronal injuries by the excessive release of During an ischemic stroke, glutamate goes into the brain parenchyma [4,5,6]. The reduction in the amount of blood glutamate results in the transportation of glutamate from the to peripheral blood from brain(according to gradient of concentration) to the levels of AST and ALT,

thereby exerting a neuroprotective impact in patients with AIS. [7,8].

The Previous research has shown that AST is associated to the of the cerebral infarct and after-AIS hemorrhagic transformation [9,10]. The Aspartate transaminase/Alanine Transaminase ratio reflects the concurrent modification of the AST and ALT ratios as a routine non-invasive laboratory examination (De Ritis ratio, AAR). It was used in deep vein thrombosis and non-alcoholic fatty liver to measure the risk of critical limb ischemia. It was managed as a prognosis,

## 2. PATHOPHYSIOLOGY OF ISCHAEMIC STROKE

A rapidly developing, complex sequence of events includes acute ischaemic stroke, including intravascular, endothelial, neuronal, glial, and inflammatory changes that either lead to cell death or resolve with the survival of a functional neuron. Whereas some cells may die immediately, if treatments to enhance perfusion and preserve cell function are prescribed quickly, other dysfunctional neurons may survive. Time is truly a vital component of the acute ischaemic stroke path. The interpretation of the sequence of events following the thromboembolic occlusion of a brain artery leading to neuronal death continues to evolve rapidly. Scientific developments offer new insights into a variety of cellular phenomena that arise during ischaemia.1 A crucial foundation for the modern approach to acute ischaemic stroke is the theory of the ischaemic penumbra. A brain center can have an irreversible neuronal damage due to profound hypoperfusion and cell dysfunction following arterial occlusion. This brain tissue center is gradually becoming necrotic and unsalvageable. While the center of fully ischaemic tissue has substantially decreased adjacent cerebral blood flow and metabolic activity, partially ischaemic tissue (penumbra) has borderline blood flow and metabolic function levels. Fortunately, in the environment of acute ischaemic stroke, the region of dysfunctional but not dead brain tissue can be reasonably wide. Potentially, the

penumbra can encompass the majority of the affected brain region. With restitution of sufficient perfusion, unstable borderline areas have the capacity for rehabilitation or institution of interventions to halt the metabolic effects of ischaemia. Conversely, these tissues could progress to cell death if flow is not restored or if the metabolic effects of ischemia cannot be reversed.<sup>1</sup> Normally, cerebral blood flow is approximately 50-55 ml/100g/min. A sophisticated autoregulatory mechanism maintains relatively constant flow despite a wide range of changes in arterial blood pressure. Autoregulation is lost in patients with ischaemic stroke, and flow becomes pressure dependent. Drop in pressure, vascular narrowing, and changes in the blood's rheological characteristics contributed to a decline in blood flow. With reductions in flow, neuronal electrical activity is disturbed. As flow declines to a rate of approximately 20-30 mL/100g/min, metabolic activity slows and intracellular acidosis occurs. At lower levels, neuronal metabolic function and intracellular water and ion homeostasis become disordered, neurotransmitters are released, and structural changes appear within the cell. The result is neuronal death.

A diagnosis for abnormalities such as non-metastatic renal cell carcinoma and carcinoma of urothelial of the upper urinary tract. [11,12,13] AAR is used to anticipate the AIS prognosis. An AIS risk model has been incorporated with this ratio [14,15,16] to determine the degree of functional freedom in everyday life. The updated Rankin Scale (mRS) is commonly used for behaviors in stroke patients. In the literature focused on the prognosis of stroke, it was mostly used.

## 2.1 Background

De Ritis ratio that is AST/ALT ratio is recently been observed to be associated in a patient's outcome for many illness. goal of the current research will be for identifying the correlation of De Ritis ratio at admission then patient prognosis in an acute ischaemic stroke at 3 months.

## 2.2 Objectives

- Analysis of the link between AAR value and disease austerly at entry, as shown by scale of National Institutes of Health Stroke.

- Using the mRS score to assess the possible association of AAR with AIS prognosis after 3 months.

## 2.3 Methodology

An observational cross sectional study will be carried out in AVBRH, a tertiary care hospital situated in the rural area of Wardha District.

The current study will be conducted on all patients with acute ischaemic stroke admitted to the M.I.C.U/CASUALTY/NEURO ICU of AVBRH of Jawaharlal Nehru Medical College, Sawangi, Wardha, who will meet the study selection criteria.

Period: The duration of the studies will be between 2020 and 2022.

## 2.4 Criteria for Inclusion

- Patients that have signs and are reported to have an acute ischaemic stroke of some kind.
- Patients diagnosed with brain CT or MRI in accordance with
- Patients with the first ischemic stroke episode will be enrolled in the study in first week of the start of stroke.
- Patients who have given permission.

## 2.5 Criteria for Exclusion

- Extreme liver conditions, disorders of the kidney or blood
- Previous impairment from stroke
- Cancer of the liver
- No functional findings after 3 months after stroke

## 3. METHODS

### 3.1 Diagnostic

Patients that have displayed signs suggestive of acute ischemic stroke at the Medication Intensive Care Unit / CASUALTY / NEURO ICU will be examined. A detailed history will be taken from the patient and the appropriate clinical review will be carried out. A comprehensive laboratory examination involving hematological and biochemical work including hemoglobin, platelet count, total leukocyte count, and serum bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, and

blood urea levels will be performed in all patients. These laboratory values will be determined for each patient, such as the AST/ALT ratio.

For confirmation of the diagnosis, all patients will undergo CT SCAN or MRI assessment. The primary results of stroke severity on admission will be obtained according to the NIHSS scale. The ranking for NIHSS would be dichotomized to less than 5 and more than 5. For all cases diagnosed with acute ischemic stroke, AST/ALT RATIO will be computed.

### 3.2 SCORE of mRS

0- SYMPTOMS NOT PRESENT AT ALL

1- NO DISABILITY SIGNIFICANT. CAN CARRY OUT FULL NORAML ACTIVITIES, despite SOME SYMPTOMS MIGHT PRESENT

2- MINIMAL DISABILITY. WITHOUT ASSISTANCE, CAN ABLE TO LOOK AFTER OWN AFFAIRS,BUT UNABLE TO CARRY OUT ALL PREVIOUS ACTIVITIES

3- DISABILITY MODERATE. Requires some help, but can walk unassisted.

4- MODERATE SEVERE DISABILITY. UNABLE WITHOUT ASSISTANCE AND UNABLE TO WALK UNASSISTED TO ATTEND OWN BODILY NEEDS

5- SEVERE DISABILITY. REQUIRES BEDRIDDEN, INCONTINENTENT, CONSTANT NURSING CARE AND ATTENSTION

6- DEAD, DEAD

NATIONAL INSTITUTE OF HEALTH STROK SCALE {NIHSS}

1A CONCIOUSNESS Degree

1- DROWSY

2- OBTUNDED

3- UNRESPONSIVE/COMA

1B QUESTIONS' ORIENTATION

0-CORRECTLY ANSWER BOTH

1-Answers one rightly

2-ANSWRESSES NEITHER RIGHTLY

1C Answers AT COMMANDS

0-PERFORMS CORRECTLY All Mission

1-PERFORMS CORRECTLY ONE Job

2-NEITHER-PERFORMS

2 GAZE

0-HORIZONTAL Natural Motions

1-GAZ PALSY PARTIAL

2-PALSY Full GAZE

3 VISUAL Areas

0- No FIELD Optical DEFECT

1- HEMIANOPIA PARTIAL

2- HEMIANOPIA Total

2- HEMIANOPIA BILATERAL

4-MOVEMENTS FACIAL

0-NORMAL NORMAL

1-FACIAL Mild Vulnerability

2-FACIAL WEAKNESS PARTIAL

3-COMPLETE PALSY UNILATERAL

5-FUNCTION OF MOTOR (ARM)

0-NO DRIFT Just

1-DRIFT 10 SECONDS Until

2 FALLS AGAINST 10 SECONDS

3-NO EFFORT Against GRAVITY

4-NO MOVEMENTATION

A-LEFT B- RIGHT-RIGHT

6-LEG'S MOTOR Working

0-NO DRIFT Just

1-DRIFT AGAINST 5 SECONDS

2-FALLS AFTER THAN 5 SECONDS

3-NO EFFORT Against GRAVITY

4-NO MOVEMENTATION

A-LEFT B- RIGHT-RIGHT

7-ATAXIA LIMB

0-NO ATXIA ONE

1-IN ONE Leg ATAXIA'

2-IN ONE LIMB ATXIA

3-IN TWO LIMBS ATAXIA

SENSORY 8

0- No LOSS Sensory

1- MILD Lack OF SENSORY

2- Extreme LOSS SENSORY

9 Expression Language

0- NORAMAL NORAMAL

1- APHASIA Moderate

2- APHASIA Serious

3- GLOBAL APHASIA OR MUTE

ARTICULATION 10

0-NORMAL NORMAL

1-DYSARTHIA MILD

2-DYSARTHIA Serious

11 INATTENTION OR EXTINCTION

0- ABSENT The

1- Moderate Depletion OF 1 MODALITY of SENSORY

## 2- Serious Depletion OF 2 MODALITIES SENSORY

### 3.3 Data Selection

The following details will be gathered:

- 1) data on demographics, including age and sex;
- 2) vascular risk factors, including current smoking and alcohol use,
- 3) previous "hypertension," "diabetes mellitus (DM)" and "dyslipidemia" history;
- 4) criteria measured for admission: "systolic and diastolic blood pressure", "Glasgow Coma Scale (GCS) score", symptom time of onset (OTT);
- 5) levels of blood serum-AST and ALT in laboratory tests;

### 3.4 Following Up

The secondary outcome of the mRS score will be measured with scores of 0-2 as a positive outcome at 3 months after stroke and 3-6 as a bad outcome. [17,18] The Data from mRs after discharge will be collected by phone.

Sample Size: Formula of Sample Size in Cross Sectional Study:

### 3.5 Sample Size

$$N = Z^2 p(1-p) / d^2$$

Where: Where:

Z = value of Z (e.g. 1.96 for 95 percent confidence level)

P = picking a preference percentage, expressed as decimal

D = trust interval, expressed in decimal form,

P = Acute ischemic stroke prevalence = 4.24 percent = 0.04244 = 0.04244 percent

D = Desired margin error = 5 percent = 0.055 margin error =

$$N = 1.962 * 0.0424 * (1 - 0.0424) / 0.0524^2 (1 - 0.0424) / 0.0524$$

$$N = 62.39 = 65 \text{ study patients needed}$$

Sample Dimension = 65

## 4. EXPECTED OUTCOMES/RESULTS

The goal of this analysis is to estimate the correlation between poor acute ischemic stroke outcomes and the AST/ALT ratio. According to previous research, the rise in AAR at admission in patients with first-ever AIS at 3 months was found to be correlated with a bad outcome. The maximum AAR cut-off was based on an interpretation of the ROC curve of 1.53. The

related delivery of serum "AST and ALT" to AIS patients at admission time is an important to improve prognosis.

## 5. DISCUSSIONS

Previous studies have shown that after ischemic stroke, excessive glutamate is secreted into the extracellular space of brain parenchyma by the neurons. Glutamate Improved Cerebrospinal fluid accumulation can lead to a pronounced increased in intracellular calcium using axoneuronal damage. Glutamate to be related with bigger severity of stroke, greater amount of infarction, and weaker functional result.[3,8] The AST and ALT effects would decrease the level of blood glutamate. According to the wider glutamate concentration gradient between the brain and blood, the brain-to-blood glutamate efflux can be accelerated.[3,7] The current research is contraindicated by Campos et al as it presents a new "prognostic biomarker" (AAR). The definite authoritative theory for the correlation between "AAR" increase and poor AIS result is still unclear and therefore needs further study. This is assumed to be caused by a disparity in behavior between AST and ALT. Has been there A lot of studies show that "ALT" is mostly enriched in tissues of liver, while "AST" is commonly distributed in various organs such as the "brain", "kidney", "muscle", and "heart". AST remains in a bigger proliferative state than ALT, even as the patient's condition is worsening.[15,16,] The decline in ALT was greater than that in AST in patients with a bad outcome, leading to a higher AAR associated with a poor outcome.

The problem of acute stroke is evident from a number of GBD studies [19-21]. Khanna et. al. studied about Serum Uric acid levels in acute stroke [22]. Bawiskar et al. reported on clinico-radiological association of serum calcium, ionic calcium and albumin corrected serum calcium in acute ischaemic stroke [23]. Few of the related studies were reviewed [24-37].

## 6. CONCLUSION

Exalted AAR at admission would be related to bad end result at 3 months of age in patients with the first episode of AIS. Sufficient determination of serum "AST" and "ALT" to AIS patients on the time of admission may also be a successful procedure to improve their prognosis.

## CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval will be collected and preserved by the authors.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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