# RESEARCH ARTICLE

## PROGNOSTIC VALUE OF TLC IN ACUTE ISCHEMIC STROKE

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**ABSTRACT**

**Introduction:** Stroke is a worldwide health problem. It makes an important contribution to morbidity, mortality and disability in developed and developing countries. Stroke is one of the leading causes of death after ischemic heart disease and malignancy. White blood cells are the cells of the immune system which protect the body against both infections and foreign invaders. An elevated white blood cell count may be caused either due to an infectious, inflammatory process .Present work was conducted to address the role of TLC in acute stroke patient and its correlation with severity and outcome. **Materials and methods:** It was Hospital based randomized case control observational study in which 50 Patients of acute ischemic stroke were enrolled as cases and 50 healthy age and sex matched individuals were enrolled as controls. The study was carried out between June 2019 and November 2019. **Observation and Results:** All these 50 patients of ischemic stroke confirmed by CT and MRI were classified on the basis of severity according to NIHSS stroke classification in mild (1-4), moderate (5-15), severe (16-20) and very severe (21-42) type of stroke. TLC level of all these patients were sent at the time of admission and mean TLC levels were calculated and it was compared with both the groups and correlated with severity and outcome. **Conclusion:** From our study it can be reasonably concluded that higher the levels of TLC, the greater will be the severity of stroke and poorer will be the outcome.

## INTRODUCTION

Stroke is a world wide health problem. It makes an important contribution to morbidity, mortality and disability in developed as well as developing countries. Stroke is one of the leading causes of death after ischemic heart disease and malignancy (World Health Organization, 2004). World Health Organization defines stroke as "rapidly developing clinical sign of focal or global disturbance of cerebral function with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin (WHO, 1988)" which may be caused either due to interruption of blood supply to the brain or rupture of blood vessels of brain. According to WHO, 15 million people suffer from stroke worldwide each year. Of these, there are 5 million deaths and another 5 miliion are permanently disabled. High blood pressure contributes to more than 12.7 million strokes worldwide. In developed countries the incidence of stroke is declining due to efforts made in reducing the blood pressure and reduce smoking. However the overall rate of stroke remains high due to aging of the population. Around 70% of

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strokes and 87% of stroke realted deaths that occur globally are seen in middle and low income countries (Feigin *et al*., 2010). Stroke is one of the major killer disease worldwide and also in India and the prevelance are increasing day by day.In 1998 - 1999 a study conducted in Kolkata showed that the crude prevalence rate of stroke was 147/1,00,000 population and annual incidence rate was 36/1,00,000 population .This was further increased to the level of 262 per 1,00,000 in rural areas and 424 per 1,00,000 in urban areas in 2012 according to Indian stroke factsheet update (Jayaraj durai Pandian, 2013). On comparison of stroke rates in India and other countries, it was found that rates are two to three times higher in India. The underlying reason for this increase is not yet understood completely. Rheumatic heart disease and cortical venous thrombosis are the most important causes of stroke in young in India. This may be partially responsible for increased stroke mortality rates in India and may also account for higher rates amongst the relatively young people than compared to that of western population (Srinivasan, 1984). White blood cells (WBCs), also called leukocytes or leucocytes, are the cells of the immune system. These function to protect the body against both infections and also foreign invaders. These cells are produced and derived from multipotent cells in the bone marrow called as hematopoietic stem cells.

Leukocytes are found throughout the body, including the blood and lymphatic system (Maton, 1997). Leucocyte population can be broadly divided into five main types: neutrophils, eosinophils, basophils, lymphocytes, and monocytes (LaFleur-Brooks, 2008). The most abundant white blood cell are neutrophils constituiting 60 -70% of the total leucocyte count (Alberts, 2002). The normal white cell count is usually between 4,000 to 11,000/cumm$^3$. Leukocytosis is defined as a white blood cell count greater than 11,000 per mm$^3$ (11 ×10$^9$ per L) (The Free Dictionary, 2007; Porth, 2011). An elevated white blood cell count reflects the normal response of bone marrow either to an infectious process or an inflammatory process. Occasionally, leukocytosis is the sign of a primary bone marrow abnormality either in white blood cell production, maturation or death (apoptosis) which may be a feature of leukemic or myeloproliferative disorders. Experimental models of stroke have shown that within minutes of onset of focal ischemia there is activation of microglia.

This activation is followed by increased influx of leucocytes into the ischemic territory. However there is no consensus about the correlation between Total Leucocytes count and prognosis after onset of acute ischemic stroke. There are so many studies which show that Total Leucocytes counts are significantly elevated in Acute ischemic damage to the Brain. The present study was conducted with the aim of establishing whether there is any correlation between this acute inflammatory marker (TLC) with severity and outcome in acute ischemic stroke patients.

### AIMS AND OBJECTIVES

- Estimation of TLC in acute ischemic stroke and comparison with healthy control patients.
- To study the correlation between TLC level and severity in acute ischemic stroke patients.
- To study correlation between TLC level and short term outcome at the end of first week.

## MATERIAL AND METHODS

**STUDY SITE** - Patients admitted in various medical wards of M. B. Govt. Hospital and RNT Medical College, Udaipur

**STUDY DESIGN** - Hospital based randomized case control observational study.

**STUDY PERIOD** - All eligible 50 consecutive cases of ischemic stroke admitted in various medical wards of M. B. Govt. Hospital and RNT Medical College, Udaipur were studied from a period June 2019 to November 2019.

**STUDY POPULATION** - Patients admitted to hospital within 72 hrs of onset of symptoms of stroke with CT or MRI evidence of Acute Ischemic stroke will be included in the study. Baseline data will be collected within 24hrs of admission.

### Inclusion criteria:

- Acute Ischemic stroke patients admitted to hospital within 72hrs of onset of symptoms of stroke of both the sexes having age more than 18 yrs will be considered as cases.

- 50 healthy age and sex matched individuals who were not suffering from any inflammatory, infectious, auto immune and malignant diseases were enrolled and will be considered as controls.

### Exclusion criteria

- Patients who are having age less than 18 years
- Patients who presented with symptoms suggestive of stroke but with underlying etiology may be trauma, surgery, neoplasm, active infections.
- Patients with stroke associated with haematological diseases, inflammatory diseases, severe hepatic illness, renal diseases, acute metabolic diseases, autoimmune diseases, intoxications with cocaine and amphetamines and acute coronary syndromes.

## STUDY METHODS

All these 50 patients with history of acute stroke admitted to the various medical wards of M.B. Govt Hospital and RNT Medical College ,Udaipur were enrolled for the study after taking written consent. Detailed clinical profile of the patients were recorded on separate performa regarding general information i.e. age, sex, present and past history, history of systemic illness and a through clinical examination including detailed neurological examination was done.

All cases were evaluated clinically including diabetes mellitus, hypertension, ischemic heart disease, previous history of stroke, alcohol intake and smoking. Patients routine haematological investigations including haemoglobin, total and differential leucocyte counts, peripheral blood film examination, urine examination, blood sugar, urea, lipid profile, electrocardiogram, X-ray chest and computerized tomogram and/or MRI were performed. All these 50 patients of ischemic stroke confirmed by CT and MRI were enrolled as cases and then they were classified on the basis of severity according to NIHSS stroke classification in mild (1-4), moderate (5-15), severe (16-20) and very severe (21-42) type of stroke.

All these enrolled patients were sent for TLC at the time of admission. 50 healthy individuals age and sex matched who were having no active infections, cardio vascular disease, autoimmune disease, haematological diseases and chronic inflammatory disease were subjected to TLC measurements and considered as control. All these enrolled patients of ischemic stroke were followed up for 7 days and outcome was observed and interpreted at the end of 7 days in form of death, deterioration, no change, improved and complete recovery. Mean level of TLC in the patient group were compared with the control group.Mean level of TLC were compared with the severity of stroke and outcome

### Statistical Analysis

Summary statistics will be done by proportions, mean, median, and standard deviation. The inferential statistics will be done by, ANOVA and person correlation. All measurements will be done using SPSS version 21.0. 'p' value <0.05 will be considered as statistically significant.

## OBSERVATIONS AND RESULTS

Out of 50 cases, 32 (64%) were belonged to >60 year of age followed by 41-60 (28%) and 18-40 (8%) years age group.

**Table 1. Age wise distribution**

| Age (years) | No. of cases (n=50) |
|---|---|
| 18-40 | 4 (8%) |
| 41-60 | 14 (28%) |
| >60 | 32 (64%) |

**Table 2. Gender wise distribution**

| Gender | No. of cases (n=50) |
|---|---|
| Male | 33 (66%) |
| Female | 17 (34%) |

**Table 3. Comparison between TLC between cases and controls**

| Age Group | Mean TLC level1s controls | Mean TLC level cases | P value |
|---|---|---|---|
| 18-40 | 7285±1499.60 | 10225±5691.38 | 0.00496 |
| 41-60 | 11370±6273.71 | 14107.14±7334.40 | |
| >60 | -- | 13445±5946.88 | |

**Table 4. Comparison between NIHSS score and levels of TLC**

| NIHSS Score | 1-4 | 5-15 | 16-20 | 21-42 |
|---|---|---|---|---|
| No. of cases (50) | 0 | 17 | 0 | 33 |
| Increased TLC (29) | 0 | 5 (17160±2107.70) | 0 | 24 (17504.17±5302.87) |

In the present study, 33 (66%) were males and 17 (34%) were females. The above table shows the comparison between TLC levels in acute ischemic stroke and the severity of stroke as assessed by NIHS scores. The TLC levels of cases and controls were studied. The above observations were made which showed that the levels of TLC were elevated significantly in cases as compared to that of controls. The outcome was divided into death, deteriorated, no change, improved and recovery. The outcome was noted within 7 days of admission in the hospital. The cut off value for raised TLC was taken as counts more than 11,000

## DISCUSSION

Acute ischemic stroke is a major cause of disability and deaths in our country. With the advent of promising therapies for acute ischemic stroke, there is higher expectation for rapid recovery and good outcome. In spite of these new therapies, prognosis is still not very good which may be because of the fact that its outcome may be influenced by many factors like extent of brain injury, severity and duration of insult as well genetic predisposition, temperature, blood glucose and various other unknown factors. Globally, stroke is the third commonest cause of moratlty (Warlow, 2003) and fourth leading cause of disease burden (Strong, 2007). An increase in the number of leukocytes above the normal range is called leukocytosis. It may be normal when it is part of healthy immune responses, or occasionally abnormal, when it is neoplastic or autoimmune in origin. A decrease below the lower limit is called leukopenia. The name "white blood cell" is derived from the physical appearance of a blood sample after it is subjected to centrifugation.

White cells are found in the buffy coat, a thin white layer of cells between the s red blood cells and the plasma. It is coined from Greek literature leuk- meaning "white" and cyt- meaning "cell". All leucocytes are nucleated. Leucocytosis can be broadly divided as neutophila, lymphocytosis, monocytosis, basophilia and eosinophilia (Zorc, 2009). Various studies prove that TLC levels are also increased in acute stroke .We studied the plasma concentration of TLC in patient of acute ischemic stroke and correlated its level with severity and outcome of3stroke. In present study 100 subjects (50 patients and 50 controls) were included who suffered from acute ischemic stroke confirmed by clinical examination and CT scan or MRI. The concentrations of TLC were measured in all patients. In our study 64%(32 patients) of the patients belonged to the age group of above 60 yrs with 28% (14 patients )belonging to the age group between 41 to 60yrs.Only 8%(4 patients) of the total population belonged to less than 40yrs.This indicates that the most common age of presentation of stroke is old age that is above the age of 60.Margaret Kelly Hayes et al[14] 2011 found that the risk of stroke doubles with each decade after 45 yrs and over 70% of all strokes occur above the age of 65.Similar findings were noted by Brett M.Kissela et al 2012 and Meaghan Roy-O'Reilly et al 2018. Regarding the influence of sex, we found that 66%(33 patients) of the total cases were male and 34%(17 patients) of the total cases belonged to the female community. Among the females affected ,all of the belonged to post menopausal age. Thus maximum number of affected patients were males. This finding is accordance with the study conducted by Roy A M Haast et al. (2012) who found that premenopausal woman are protected from stroke and other cardiovascular events due to the presence of estrogen.

However after menopause they are affected by stroke at a similar incidence as compared to the male community. Yali Wang et al 2019 also noted the similar findings. The comparison between the mean TLC levels of cases and controls was studied. In the age group of 18-40, The mean TLC levels in controls was 7285±1499.60 while that in cases was 10225±5691.38 respectively. In the age group of 41-60,the mean TLC levels in controls was 11370±6273.71 while that in cases 14107.14±7334.40. Above the age group of 60, the mean TLC in controls were zero as no subjects in this age group were studied while that in cases 13445±5946.88. The p value was calculated. The p value between mean levels of TLC between cases and controls was 0.00049. It was found to be statistically significant at<0.05. From this we can conclude that TLC levels are raised significantly in patients of acute ischemic stroke as compared to the normal healthy controls. R Kazmierski et al in 2001 also published the same findings and proposed that leucocytosis is commonly observed in stroke and is considered as a poor prognostic marker in stroke. In our study, the severity of stroke was classified according to NIHSS stroke classification in mild (1-4), moderate (5-15), severe (16-20) and very severe (21-42) type of stroke. Among the 17 patients with score between 5-15(moderate stroke) 5 patients had raised TLC. The mean TLC was 17160±2107.70. In the 33 patients with score between 21-42 (very severe stroke) 24 patients had raised TLC. The mean TLC in this group was 17504.17±5302.87.The p value was calculated between both groups. It was 0.00023 when then mean TLC levels of NIHSS 21 – 42 group was compared with that of group with scores 5 - 15.Andre D. Kumar et al 2012 compared the levels of TLC evaluated at the time of admission of stroke with the NIHSS scores.

**Table 5. Outcome in relation to TLC**

| TLC | No. of cases | Outcome | | | | |
|---|---|---|---|---|---|---|
| | | Death | Deteriorated | No change | Improved | Complete recovery |
| 4000-11000 (7354.76 ± 2019.54) | 21(42%) | 4(19.04%) | 4(19.04%) | 1(4.7%) | 11(52.3%) | 1(4.7%) |
| >11000 (17451.85 ± 4995.43) | 29(58%) | 12(41.3%) | 7(24.13%) | 3(10.3%) | 4(13.7%) | 3(10.3%) |

They finally found leucocytosis at the time of stroke correlates with poor functional outcomes and may represent a marker of increased cerebral damage because of increased parenchymal inflammation. The association between raised total leucocyte count and outcome of stroke was studied. The cut off value for raised TLC was taken as counts more than 11,000.The observations were made. The total number of cases with raised TLC were 29(58%).Out of this, there were 12(41.3%) deaths,7(24.13%) cases showed deterioration in condition,3 (10.3%)cases had no change. Improvemnt was seen in 4(13.7%) cases while complete recovery was seen in 3(10.3%) cases. The poor outcome was considered as those cases that died or got deteriorated. The mean TLC levels were 7354.76 ± 2019.54 in group with normal TLC and 17451.85 ± 4995.43 in group with raised TLC. The p value was calculated between both groups. The p value was 0.00040.The result is significant at p value <0.05.

Furlan *et al*. (2014) found that in patients with ischaemic stroke, elevated white blood cell count (WBC) has been associated with stroke severity on admission and poor functional outcome. He hypothesized that higher WBC is an independent predictor of stroke severity, greater degree of disability and 30-day mortality after acute ischaemic stroke. Patients were divided into groups as follows: low WBC (0.1-4 × 10(-9) /l), normal WBC (4.1-10 × 10(-9) /l) and high WBC (10.1-40 × 10(-9) /l). Primary outcome measures were the frequency of moderate/severe strokes on admission (Canadian Neurological Scale ≤ 8), greater degree of disability at discharge (modified Rankin score 3-6) and 30-day mortality. In total, 8829 patients were included. After adjustment for major potential confounders, every 1 × 10(-9) /l increase in WBC was associated with stroke severity on admission [odds ratio (OR) 1.09; 95%CI 1.07-1.10; P < 0.0001), disability at discharge (OR 1.04; 95%CI 1.02-1.06; P = 0.0005) and 30-day mortality (hazard ratio 1.07; 95%CI 1.05-1.08; P < 0.0001). The Kaplan-Meier curves indicate that elevated WBC is associated with higher mortality after acute ischaemic stroke (P = 0.001).They finally concluded that in patients with acute ischaemic stroke, higher WBC on admission is an independent predictor of stroke severity on admission, greater degree of disability at discharge and 30-day mortality.

## Conclusion

From the present study we can conclude that the TLC levels are usually significantly high in cases of acute ischemic stroke patients as compared to that of normal healthy population and the levels of TLC at the time of admission of stroke will predict the outcome and severity of stroke.

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