Abstract: Albumin is a potent neuroprotective protein capable of influencing the disease process in Stroke. However, this neuromodulation has not been well documented in black African patients. This study was aimed at determining the association between plasma Albumin levels and outcome of Stroke in adult patients and the possible use of plasma Albumin level as a prognostic indicator in Stroke. Methods: Sequential first episode acute Hemorrhagic and Ischemic Stroke patients were enrolled into the study between December 2016 and May 2017. Neurological examinations were based on the National Institute of Health Stroke Scale (NIHSS). Admission plasma Albumin levels were measured using electrophoresis and CT scan imaging done. All parameters were assessed on day 0, 3, 5, and discharge from hospital and on follow-up for 2 weeks (total duration of 6 weeks). The outcome measures were 6 weeks mortality and functional outcome which were scored using the modified Rankin scale (mRS) and modified Asthworth score.

Results: A total of 50 acute Stroke participants were studied. The mean age was 54.30 ±14.25 years. Ischemic Stroke accounted for 62% of participants whereas 38% had Hemorrhagic Stroke. While 38% of Hemorrhagic Stroke participants died between day 3 and 13 (mean 7.34±3.86 days) of Stroke occurrence, only 9.7% of Ischemic participants died during the same period. The 6 weeks mortality rate was 16% in participants with hypoalbuminemia compared to 2% in participants with normal Albumin. Albumin levels in the range of 20 to 30mg/ml (OR, 2.67; 95% confidence interval, 1 to 10) and a drop of more than 10mg/ml from admission to outcome was noted in those who died. Albumin Decrease Index (ADI) of 0.942, mean NIHSS of 8.76±4.25 and mRS 3.28±1.43 (p=0.0001) were associated with poor outcome.

Conclusion: Albumin was significantly low with a high ADI in Stroke participants with a poor outcome. Patients with hypoalbuminemia are more than twice at risk of having a poor outcome. There was no difference in the ADI between Hemorrhagic and Ischemic stroke suggesting that Albumin is a good predictor of outcome in both types of Stroke.

Key words: Electrocardiography, Hemorrhagic Stroke, Ischemic Stroke, hypoalbuminemia, Neuroprotective.
1.0 Introduction: Albumin is a potent neuroprotective protein capable of influencing the disease process in Stroke. However, this neuromodulation has not been well documented in black African patients. This study was aimed at determining the association between plasma Albumin levels and outcome of Stroke in adult patients and the possible use of plasma Albumin level as a prognostic indicator in Stroke. Stroke is a focal neurological deficit of sudden onset secondary to a cerebral vascular event. The clinical syndrome of Stroke is characterized by acute loss of focal brain function lasting more than 24 hours or leading to death due to either inadequate blood supply or hemorrhage to a part of the brain. It is an important public health problem. Stroke is also referred to as a Cerebral Vascular Accident (CVA) as it involves sudden death of some brain cells due to lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain. Worldwide, CVA or Stroke has the highest rates of mortality and disability adjusted life years lost amongst the non-communicable diseases. It is estimated that 750,000 new Strokes occur annually in the USA resulting in 150,000–200,000 deaths. In Zambia, Stroke is the fifth highest cause of death contributing 4% of total deaths (119.93 deaths per 100,000) annually. There are two major types of Stroke; Ischemic and Hemorrhagic. Ischemic Strokes include cryptogenic, lacunae and thromboembolic, caused by obstruction of blood flow to an area of the brain and are said to account for 87% of all Strokes. Hemorrhagic Strokes account for the remaining 13% of all Strokes, and are due to a lack of blood flow to an area of the brain that is triggered by spontaneous rupture of a blood vessel causing hemorrhage into or over the brain substance. The Hemorrhagic Strokes are primary intracerebral haemorrhage, intraventricular haemorrhage and subarachnoid haemorrhage.

A recent cohort study at UTH showed that Stroke is an important cause of admission and death. In addition, it was noted that it occurred in relatively young patients compared to the developed world with, 65% Ischemic and 35% Hemorrhagic type. Since Ischemic Strokes account for most of all Strokes, advances in the diagnosis and medical treatment of Strokes have focused predominantly on Ischemic Stroke. However, Hemorrhagic Stroke is the most severe form with a poor prognosis.

In Zambia, the incidence of Stroke has increased because of the combination of dietary problems, high prevalence of smoking, dyslipidemia, Diabetes Mellitus (DM) and hypertension. The other cause is due to the advent of HIV and AIDS pandemic which has brought in a new dimension to risk factors of Stroke. Stroke mechanisms do vary in HIV-infected patients, with a relatively high incidence of vasculitis and hypercoagulability. Opportunistic infection associated with HIV, have also been said to cause Stroke. HIV-associated vasculopathy describes various cerebrovascular changes, including stenosis and aneurysm formation, vasculitis and accelerated atherosclerosis might be caused either directly or indirectly by HIV infection.

Stroke is a complex pathophysiological process involving; energy failure, imbalance of ion homeostasis, acidosis, intracellular calcium overload, neuronal excitotoxicity, free radical-mediated lipid oxidation, inflammatory cell infiltration and glial cell activation. These events ultimately lead to neuronal apoptotic cell death or necrosis. In Stroke survivors, there is a high rate of CVA recurrence. Mostly, efforts to curb Stroke
have been mainly focused on identification of modifiable risk factors as effective Stroke prevention to reduce mortality rate. Of recent importance in neurophysiology is the neurochemistry of Albumin as an antioxidant and neuroprotective substance. At University Teaching Hospital (UTH), there is a limited set of interventions for treating Stroke in its initial phases and prevention of further neuronal damage and as such early detection of determinants of this disease process are essential.

**Statement of the problem:** When blood flow to the brain is interrupted, in acute Stroke, some brain cells die immediately, while others remain at risk of dying. These damaged cells make up the Ischemic penumbra and can linger in a compromised state for several hours. With timely treatment these cells can be saved but failure to do so results in brain injury which becomes irreversible within little time as an hour. In humans, brain damage begins from the moment the Stroke starts and often continues for days thereafter. Physicians now know that there is a very short window of opportunity for treatment of the most common form of Stroke. Most if not all the patients presented to UTH, being a tertiary hospital, present late after delays at home and primary health facilities. These patients need modalities that can enable physicians to choose the best treatment options guided by markers of the disease process.

Initial management of acute Stroke includes; imaging to classify the Stroke type, followed by a therapeutic plan. The type of Stroke therapy a patient should receive depends upon the stage of the disease. Generally there are three treatment stages for Stroke: prevention, therapy immediately after Stroke, and Post-Stroke rehabilitation. Therapies for Stroke include medications, surgery, or rehabilitation. The most popular classes of drugs used to prevent or treat Stroke are antithrombotics (antiplatelet agents and anticoagulants) and thrombolytics. Recently neuroprotectants, medications that protect the brain from secondary injury caused by Stroke have been introduced. There are several different classes of neuroprotectants that show promise for future therapy, including Human Serum Albumin (HSA), glutamate antagonists, antioxidants, apoptosis inhibitors, and many others. It can therefore be noted that understanding the relationship between plasma Albumin and outcome of acute Stroke is of cardinal importance in the course of disease process. In literature reviewed low plasma Albumin levels less than 35mg/ml at the onset of a Stroke has been associated with poor outcome such as long term disability.

For most Stroke patients, physical therapy (PT) is the cornerstone of the rehabilitation process. A physical therapist uses training, exercises, and physical manipulation of the Stroke patient’s body with the intent of restoring movement, balance, and coordination. The aim of PT is to have the Stroke patient relearn simple motor activities such as walking, sitting, standing, lying down, and the process of switching from one type of movement to another. At UTH the main stay of treatment is medical and PT with limited success rate.

The above mentioned is a very expensive endeavor, costing approximately USD 43 billion per annum as it can be seen in the illustration of the costs in the USA as estimated by the National Institute of health services (NIHMS). Initial admission accounts for 43% rehabilitation and physician costs are 30% while the remaining is shared by medication and readmission costs.

While a study showed that Stroke is a significant cause of morbidity and mortality at the UTH, with Ischemic type predominance, no observational study has been carried out at the UTH and in Zambia. At present, there is no evidence regarding use of physiological markers e.g. Albumin in monitoring and predicting clinical outcome of acute Stroke.

**1.2 Hypothesis**

- Low plasma Albumin levels are associated with poor outcome of Stroke in adults patients
Plasma Albumin levels can be used as a prognostic indicator in patients with Strokes.

1.3 Study justification: Although Stroke is a disease of the brain, it can affect the entire body. Some of the disabilities that can result from a Stroke include paralysis, cognitive deficits, speech problems, emotional difficulties, daily living problems and pain\textsuperscript{9,12,23}. All Strokes are different. They leave varying effects such as relatively minor to more serious long term problems. The burden of Stroke impairs quality of life and a potential economic drawback.

A snap check of the burden of Stroke at UTH, from January to June 2016 reviewed that, 24.9\% of 213 patients admitted to UTH (2016 Mid-year audit) died while a 58\% had permanent disability. By the end of 2016, incidence of Stroke was 37.8\% compared to 32.3\% in 2015. With this fact in mind new treatment modalities are needed. However, in order to put in place new management strategies and reduce Stroke morbidity and mortality, this study on the association between plasma Albumin and Stroke outcome in adult patients admitted to UTH was of great necessity. This study would help open up way for Albumin therapy in acute Stroke and possibly enlighten clinicians on the need to assess patients for determinants of Albumin production and losses as key markers in the prognosis of Stroke in admitted patients. Unique to this study was that it looked at both types of Stroke and that future implementation need not expensive investigative techniques such as Computerized Tomographic Scan (CT-Scan) to distinguish between Hemorrhagic and Ischemic Stroke as the case in the current modalities. Improved knowledge about the mechanisms and causes of Stroke would lead to improved investigation and treatment of patients.

1.4 General objective: To determine the association of plasma Albumin levels and outcome of Stroke in adult patients with acute Stroke.

1.5 Specific objectives
1. To determine the plasma Albumin levels in Ischemic and Hemorrhagic Strokes in adult patients
2. To determine the clinical outcome of Stroke in relation to plasma Albumin levels in adult patients

2. Research Methodology: The research was designed with the aim of determining the association between plasma Albumin levels and outcome of Stroke in adult patients with acute Stroke using clinical and biochemical parameters.

2.0 Study Design: An analytical study was conducted on adult in-patients diagnosed with first ever acute Stroke at admission and followed up until a Stroke outcome.

2.1 Study Site: This study was conducted in Medical Admissions Ward, Adult Medical Emergency Unit and E-block medical wards at the UTH in Lusaka.

2.2 Study Population: Lusaka is the capital and largest city in Zambia and one of the fastest-developing cities in Africa with a population of about 2,191, while its urban population is 2.4 million. It has a land area of 21,896 sq.km. It has an unemployment rate of 31\%. The population density is 100 people per square km. The sex ratio (female per 100 males) is 102.33\textsuperscript{57}. The average household size is 4.9 and a total of 444,418 households. Life expectancy is 51. The health system is funded by the government and supported by donors. There are 231 doctors. The population is mainly average income earning and a mixed education background. The UTH is the national referral hospital\textsuperscript{57}.

2.3 Target Population: All adult patients admitted to the UTH Adult Emergency unit (AMEU) and E-block wards between December 2016 and May 2017.

2.4 Sampling: Systematic purposeful sampling was used. This is a non-probalistic sampling where adult patients with Stroke were looked for in the emergency medical admission ward and Adult medical Emergency unit and E-block and recruited if they met the criterion.
2.5 Sample size: Sample size was determined based on the Confidence Interval (CI) for incidence and significance level of 0.05. In 2015 the total number of patients seen with Diabetes Mellitus (DM) and hypertension (HTN) was 1497 (i.e. population at risk). The incidence was 32.3 percent, giving us the upper limit of the CI. The lower limit was 19.2 percent based on the incidence of Stroke in males. Based on this the sample size estimate was 55 patients.

Inclusion criteria
1. All first acute Strokes within 72 hours, confirmed by imaging studies of the head (Magnetic Resonance Imaging or Computed Tomography).
2. Age >18 or <75 years of either sex
3. Informed consent

Exclusion criteria
1. Traumatic Stroke
2. Acute renal failure on admission
3. Use of B vitamin or Statin therapy within two weeks prior to hospital admission
4. Severe heart failure
5. Pregnancy
6. Liver failure
7. Previous history of Stroke

Control group
All patients who have fulfilled the recruitment criterion and have normal serum Albumin. These were unmatched control for each Stoke type.

2.6 Clinical procedure
When a possible Stroke patient arrived at the hospital, the attending physician took history and performed a general and neurological examination to confirm the Stroke (diagram 3.1).

Diagram 1: Approach to a participant

Suspected Stroke

Confirmed Stroke

Consent

NO

YES

Recruitment

CT Scan

Laboratory

Hemorrhagic

Alb Normal

Alb abnor mal

Outcome

Ischemic

Alb normal

Alb abnormal

Outcome

NB. Alb= Albumin.
Outcome measure on a scale of one to six using mRS

Consent: Informed consent was obtained from would be participant and or next of kin to be enrolled in the study in accordance with the Helsinki declaration.

The participants were evaluated to obtain demographic data, symptoms and signs. Symptoms included:

- Sudden numbness or weakness or altered sensorium in the face.
- Sudden confusion, difficult in speaking, or understanding speech.
- Sudden onset of visual disturbance in one or both eyes. Recent blackout.
- Sudden failure in walking, dizziness, loss of balance, or lack of coordination.
- Sudden severe headache of known cause.

The Cardiovascular System (CVS) was examined to look for signs of heart failure, valvular lesions and stigmata of chronic HTN. Arterial HTN was diagnosed and documented in medical records. It was defined as at least two readings of blood pressure were >140mm Hg (systolic) or >90mm Hg (diastolic) after the acute phase of stroke or known patient on antihypertensive treatment. Categories of HTN based on blood pressure values applied were as below:

- Category 1 (mild): systolic 140 – 159, diastolic 90 - 99
- Category 2 (moderate): systolic 160 – 179, diastolic 100 - 109
- Category 3 (severe): systolic > 180, diastolic >110

DM was diagnosed if its presence was documented in medical records or patient was taking Insulin.

The participant’s neurological deficits were assessed and the admission National Institutes of Health Stroke Scale (NIHSS), modified Rankin stroke scale (mRS), modified Ashworth score (mAS) recorded at day zero (0), three (3), day five(5), discharge and two weeks after discharge ( at review).

Laboratory: Five milliliters of venous blood samples were obtained on 0, 3, 5, discharge and follow-up days of acute Stroke for the measurement of Albumin.

Within 2 hours of blood collection, Levels of plasma Albumin, total protein, liver function and renal function tests were measured for the exclusion criteria and reducing the probability of an error.

Plasma Albumin and total protein levels were measured at admission, day 3, day 5, discharge and at two weeks follow up concomitant with the mRankin. After collection, the blood samples were placed into plasma separator tubes with K2-EDTA and serum separator tubes for centrifugation and Albumin levels were evaluated using electrophoresis (Beckman Instruments, Fullerton, USA).

Radiology: A CT-scan was done on each patient according to attending unit physician’s request and hospital policy using the Siemens Somatom sensation open CT-scan. The equipment is available at the UTH radiology department. CT- scan reports were done by a radiologist. Based on the CT- scan, the type of Stroke was established as Ischemic or Hemorrhagic. For some patient who arrived within 6 hours of the Stroke event CT-scan was repeated after 12 hours.

2.7 Data collection: Data was collected using a questionnaire tailored to extract information concerning patient’s social demographic factors, risk factors, general and neurological examinations; NIHSS score; mRS score; and modified Ashworth’s score. Laboratory measurements of plasma Albumin and total protein were recorded. All the data was checked for completeness and entered onto a Microsoft Office access form.

Variables: The dependent variable was plasma Albumin levels and the outcome of Stroke (modified Rankin scale score and Ashworth score). Modified Rankin scale score (mRS) was be described in terms of good (mRS ≤2), dependence (mRS ≤3), severe (mRS 4-5), death (mRS) 6.
Plasma Albumin was a continuous variable to be measured in milligrams per milliliter (mg/ml). The normal plasma Albumin level was 35-55mg/ml\textsuperscript{14}. The independent variables were: risk factors, Adult malnutrition, dehydration, raised platelets, raised MCV.

- Outcome variable (dependent): The outcome variable was Stroke. This was a categorical variable (Haemorrhagic or Infarct). Proportions and percentages were used to describe it.
- Potential confounders: Age, sex, urea, creatinine, e.g. age were potential confounders. As continuous variables, these were described using median, inter-quartile ranges (and also range for age). Obesity was also treated as a potential confounder though it might be an effect modifier.

2.8 Data Analysis methods: Collected data was transferred from Microsoft Access form to SPSS 2015 version 23.0 for analysis. Summary results are as below presented in figures and tables.

Descriptive statistics: Albumin was described using median and interquartile ranges. Analytical statistics: To determine the relationship between plasma Albumin and Stroke severity, multiple logistic regression analysis models with mRS, as the outcome variable and Albumin and NIHSS as the independent variables. Stroke outcome was in terms of type, severity and/or death. Potential confounding was checked by a step-by-step inclusion of variables. A significance level of 0.05 was used to include or exclude factors in the final equation. Interactions were also checked. Pearson’s rank correlation was also applied to calculate the relationship between biochemical parameters and CT-scan findings or NIHSS values. Statistically significant values were considered when \( p \)- value was <0.05.

2.9 Ethical considerations: The clinical study was based on a normal hospital setup and no procedure was done outside the hospital protocol. All patients had a right to confidentiality. All tests done were part of the routine clinical examinations and that no discomfort was caused to the patients. This proposal was approved by the University of Zambia (UNZA) Biomedical Research Ethic Committee (UNZA/BREC) and UTH Management and the department of physiological sciences taking into account the Helsinki declaration\textsuperscript{50}.

3.0 Results: Biochemical and clinical characteristics of acute Stroke participants were measured and analyzed using multiple logistic regression model, Pearson’s correlation test and, ADI estimated using the Laspeyre’s index formula. A total of fifty-five (55) acute Stroke patients were enrolled into the study and followed up for 6 weeks from December 2016 to April 2017. Five (5) of the participants were excluded out of the analysis because four (4) had withdrawn consent on follow-up whilst one (1) was lost on follow up. Only 50 were included in the analysis (table 3.1).

The age range was from 22 to 75 years with a mean of 54.30 ±14.25 years with a male to female ratio of 1.17:1. The Stroke distribution was such that sixty-two percent (62%, that is 31 participants consisting of 12 females and 19 males) had ischemic Stroke whereas 38% (19 participants; 11 females and 8 males) had hemorrhagic Stroke (table 3.1). It was found that, 54% (27) of the participants had moderate to severe hypertension at admission and of these, only 74% (20) were known hypertensive patients. The remaining 46% (23) were normal tensive with 73.9% (17) of them being known hypertensive. Figure 3.1 illustrates the risk factor profile in each Stroke type. Severe hypertension was by far more in Hemorrhagic than Ischemic Stroke (figure 3.1). Hemorrhagic Stroke was female predominant in contrast to Ischemic type. Diabetes and HIV were only noted in Ischemic type.
About 80% (40) of the total participants reported to the health facility within 4 to 24hrs of a Stroke event whilst the remaining reported between 24 and 72 hours.

The estimated mean NIHSS was 8.76±4.25, mRS 3.28±1.43, Ashworth score 6.42±3.47(table 3.1).

**Table 3.1: Baseline characteristics of the patients stratified by Stroke type and gender**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hemorrhagic stroke</th>
<th>Ischemic stroke</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (N=11)</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Male (N=8)</td>
<td>8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age in years: mean (±SD)</td>
<td>58.05(±11.50)</td>
<td>52(±15.430)</td>
<td></td>
</tr>
<tr>
<td>Age range(yrs)</td>
<td>42 - 75</td>
<td>22 - 75</td>
<td></td>
</tr>
<tr>
<td>Adm BP mean (±SD) mmHg</td>
<td>168(34.3)</td>
<td>142(38.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>• SBP</td>
<td>105(21.6)</td>
<td>93(23.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>• DBP</td>
<td>0.4</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Risk factor profile; N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td>27(54)</td>
<td>4(12.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>• Diabetes</td>
<td>2(4)</td>
<td>2(6.45)</td>
<td>0</td>
</tr>
<tr>
<td>• Cigarette</td>
<td>4(8)</td>
<td>1(3.2)</td>
<td>3(9.67)</td>
</tr>
<tr>
<td>• HIV</td>
<td>2(4)</td>
<td>1(3.2)</td>
<td>3(9.67)</td>
</tr>
<tr>
<td>• Alcohol</td>
<td>6(12)</td>
<td>2(6.45)</td>
<td>0.01</td>
</tr>
<tr>
<td>• Non</td>
<td>9(18)</td>
<td>3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adm NIHSS :mean (±SD)</td>
<td>8.76±4.25</td>
<td>7.77(±3.64)</td>
<td>0.0001</td>
</tr>
<tr>
<td>mRS :mean((±SD))</td>
<td>3.28±1.43</td>
<td>3.23(1.67)</td>
<td></td>
</tr>
<tr>
<td>Ashworth score :mean((±SD))</td>
<td>6.42±3.47</td>
<td>6.29(3.26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of in hospital stay((±SD))</td>
<td>3-21 days</td>
<td>7.06(3.89)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure, DBP=diastolic blood pressure, SD= standard deviation, N=number, adm=admission
In Ischemic Stroke the Albumin decrease index (ADI) was 0.938 (4.29mg/ml) and 0.945 (4.32mg/ml) in Hemorrhagic Stroke. At p-value of 0.01 and 95% C.I, there was no difference in the ADI between Hemorrhagic and Ischemic Stroke. Forty-two percent (42%) that is 21 patients of the participants with ADI average of 0.942 (4.30mg/ml) had a poor outcome in terms of either death or severe disability in both types of Stroke (table 3.2). Outcome for Hemorrhagic Stroke was in terms of good (26.2%), dependence (31.6%), severe (10.6%) and death (31.6%), whilst in Ischemic Stroke good outcome (35.6%), dependence (19.2%), severe (35.6%) and death (9.6%) as in table 4.2. Thirty-eight percent (6) of Hemorrhagic Stroke participants died between day 3 and 13 (mean duration of stay 7.34±3.86) of Stroke occurrence unlike Ischemic were 9.7% (3). The six (6) week mortality rate was 16% in participants low Albumin compared to the 2% in controls (table 4.2).

The mean plasma albumin was markedly low in those who died in both types of Stroke (p<0.05, interquartile range 20-34mg/ml) and showed a drop in Albumin of more than 10mg/l from admission to adverse outcome (ADI 0.942). In almost all participants the admission plasma Albumin was normal but decreased levels were noted to occur on day three.

Table 3.2: Biochemical and clinical characteristics of the patients stratified by stroke type and outcome

<table>
<thead>
<tr>
<th>Plasma Albumin mg/dl</th>
<th>Hemorrhagic stroke</th>
<th>Ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome N (%)</td>
<td>40 - 55</td>
<td>35 - 39</td>
</tr>
<tr>
<td>Good</td>
<td>3(15.7)</td>
<td>2(10.5)</td>
</tr>
<tr>
<td>Dependence</td>
<td>1(5.3)</td>
<td>5(26.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>0(0)</td>
<td>1(5.3)</td>
</tr>
<tr>
<td>Death</td>
<td>1(5.3)</td>
<td>0(0)</td>
</tr>
<tr>
<td>mRS : mean(±SD)</td>
<td>3.84(±1.68)</td>
<td></td>
</tr>
<tr>
<td>Ashworth : mean(±SD)</td>
<td>6.63(3.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of in hospital stay(±SD)</td>
<td>7.79(3.87)</td>
<td></td>
</tr>
<tr>
<td>ADI per day</td>
<td>0.945(4.32mg/l)</td>
<td></td>
</tr>
<tr>
<td>Adm SBP mmHg:Mean (±SD)</td>
<td>142(24.2)</td>
<td>160(32)</td>
</tr>
<tr>
<td>Adm DBP mm Hg:Mean (±SD)</td>
<td>80(25.4)</td>
<td>96(30.2)</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure, DBP=diastolic blood pressure, SD= standard deviation, N=number, adm=admission, ADI= Albumin reduction index, NIHSS= national institute of Health stroke score, good= mRS ≤2, dependence= mRS ≤3, severe= mRS 4-5, death= mRS 6 , mRS = modified Rankin score.
A Pearson correlation test was run for Stroke outcome, type of Stroke, Ashworth score, NIHSS, and duration of stay (table 3.3). A significant correlation between Stroke outcome and type of Stroke was obtained \((r = -.29, CI. 95\%, 2 \text{ tailed test})\) and NIHSS \((r = -0.57, CI. 99\%, 2 \text{ tailed test})\).

**Table 3.3: Correlation test results for Stroke outcome, NIHSS, Ashworth, Stroke type and duration of stay**

<table>
<thead>
<tr>
<th></th>
<th>NIHSS</th>
<th>Type of Stroke</th>
<th>Ashworth score</th>
<th>duration of stay</th>
<th>Stroke outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIHSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>1</td>
<td>.300*</td>
<td>.047</td>
<td>.055</td>
<td>-.571**</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.035</td>
<td>.745</td>
<td>.705</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Type of Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>.300*</td>
<td>1</td>
<td>.048</td>
<td>.092</td>
<td>-.290*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.035</td>
<td>.740</td>
<td>.525</td>
<td>.041</td>
</tr>
<tr>
<td><strong>Ashworth score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>.047</td>
<td>.048</td>
<td>1</td>
<td>.177</td>
<td>.127</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.745</td>
<td>.740</td>
<td>.220</td>
<td>.378</td>
</tr>
<tr>
<td><strong>duration of stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>.055</td>
<td>.092</td>
<td>.177</td>
<td>1</td>
<td>.194</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.705</td>
<td>.525</td>
<td>.220</td>
<td>.177</td>
</tr>
<tr>
<td><strong>Stroke outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.571**</td>
<td>-.290*</td>
<td>.127</td>
<td>.194</td>
<td>1</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.000</td>
<td>.041</td>
<td>.378</td>
<td>.177</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

- \(0.1 < \mid r \mid < 0.3\) small / weak correlation
- \(0.3 < \mid r \mid < 0.5\) medium / moderate correlation
- \(0.5 < \mid r \mid \) large / strong correlation
There was no correlation between Stroke outcome, Ashworth score and duration of stay ($r=0.13$, $r=0.19$ respectively) as seen in table 3.3. This implies that duration of stay and Ashworth score are not related to the Stroke outcome.

In a multiple logistic regression (table 3.4) admission Stroke severity measured by plasma Albumin and NIHSS correlated with 6 week morbidity and mortality in the presence of other variables (HTN, age and ADI). Analysis showed that low plasma Albumin of 20-34mg/l (combined OR, 2.67; 95% CI, 1 to 10) was independently associated with poor outcome with more than twice the risk in controls.

**Table 3.4: Determinants of 6 week stroke severity and mortality using multiple logistic regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemorrhagic stroke</th>
<th></th>
<th>Ischemic stroke</th>
<th>Stroke type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Std Error</td>
<td>95% CI</td>
<td>Correlation coefficient</td>
<td>P-value</td>
</tr>
<tr>
<td>Plasma Albumin</td>
<td>-3.87</td>
<td>0.014-0.54</td>
<td>-0.174</td>
<td>0.017</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.72</td>
<td>2.132-3.842</td>
<td>-0.129</td>
<td>0.013</td>
</tr>
<tr>
<td>Age</td>
<td>-0.24</td>
<td>0.542-1.674</td>
<td>-0.302</td>
<td>0.322</td>
</tr>
<tr>
<td>ADI per day</td>
<td>0.945(4.32mg/l)</td>
<td></td>
<td></td>
<td>0.938(4.29mg/l)</td>
</tr>
</tbody>
</table>

**NB.** Combined OR, 2.67; 95% CI, 1 to 10
Hemorrhagic Stroke OR: 3, 95% CI: 1.2–10
Ischemic OR: 2.5, 95% CI: 1.0–9)

SD= standard deviation, ADI= Albumin reduction index, NIHSS= national institute of Health stroke score, Std Error= standard error. OR= Odds ratio, CI= Confidence interval

4.0 **Discussion:** This study showed changes in plasma Albumin levels in patients during acute Stroke. It was observed that there was a relationship among ADI, NIHSS score and Stroke outcome (mRS and Ashworth score) in Hemorrhagic and Ischemic type as indicated in table 3.3. A higher NIHSS and severe HTN were observed in patients with a greater ADI at day 3. All observed deaths were associated with a reduction in plasma Albumin of more than 10mg/l by day 3 and gradually there on until the time of death or severe morbidity. Fifty-five (55.5%) percent of the participants with severely low Albumin between 20 to 30mg/l died by day 3, twenty-two point two point two (22.2%) by day 7 and the remainder between day 9 and 13. This implies that seventy-six point seven percent (76.7%) of deaths occurred in the first 7 days of the acute phase of the Stroke episode. The mortality rate was at 18% in 2 weeks. The observed characteristic patterns are similar in both Hemorrhagic and Ischemic stroke, although participants with the former type had a severe form of Stroke and recorded the highest number of poor outcome. Hemorrhagic Stroke was associated with fulminant HTN, a probable covariate to poor outcome and severity. Participants with plasma Albumin <34mg/l showed marked disability and morbidity after Stroke. Plasma Albumin levels between 35 and 39mg/l were observed to be associated with dependence while plasma Albumin levels >40mg/l were associated with good outcome (table 3.2).

Numerous studies in the past have shown a strong association between serum Albumin concentrations and clinical outcome \(^1\text{,}^2\text{,}^1\text{,}^1\text{,}^1\text{,}^3\).
In a well-controlled study\textsuperscript{11} it was reported that, serum Albumin concentrations $> 35$ g/L had a $1.7\%$ mortality rate, those with concentrations $< 34$ g/L had a $25\%$ mortality rate, and those with concentrations $< 20$ g/L had a $62\%$ mortality rate values that are in line with this research’s findings. Another study reported a relation between mortality and decreased serum Albumin concentrations in undernourished elderly male patients \textsuperscript{1,13}. ADI can reflect an increase in the metabolic rate or a decrease in albumin synthesis during the acute phase of Stroke. Release of stress hormones such as glucagon, catecholamines and corticosteroids results in the intensification of numerous catabolic pathways which include proteolysis. Increased levels of corticosteroids sensitize the heart and blood vessels to catecholamines hence the raised blood pressure observed in participants with high ADI (very low plasma Albumin). Albumin is a negative acute phase protein and concentration falls between day 1 and day 7 after Stroke onset\textsuperscript{1}. These processes are connected with the degradation of plasma Albumin, which then leads to hypoalbuminemia. Low plasma Albumin levels in patients with Ischemic Stroke are associated with higher serum cortisol levels \textsuperscript{13}. The catabolic state and the associated neuroendocrine response that is likely to follow an acute Stroke may lead to altered serum Albumin concentrations and there is recent evidence linking the high stress reaction after Stroke and under nutrition \textsuperscript{1, 11, 13}. It may therefore be that in catabolic states the synthesis of acute phase proteins has priority over serum albumin suggesting that, ADI during Stroke can indirectly reflect the intensity of the response within acute phase of Stroke. This may play a part in a worse outcome after Stroke, which was confirmed in our study.

**4.1 Conclusion:** It was concluded that worsening of the neurological state and death corresponds to a decrease in serum Albumin levels during acute Stroke. Plasma Albumin levels in acute phase can be used to predict outcome of a Stroke in both Hemorrhagic and Ischemic Stroke. Plasma Albumin concentrations showed a significant and independent association with outcome measures. Stroke patients with hypoalbuminemia day 3 had an increased risk of complications and poor functional outcome during hospitalization and follow up period. The plasma Albumin concentration was a good predictor of the degree of disability and handicap at admission and also at other times of the hospital stay. Plasma Albumin concentration in the hospital was also a strong and independent predictor of mortality, as reflected by the Odds ratio.

**Acknowledgements:** Sincere gratitude to the University Teaching Hospital administration, the department of internal medicine and its adult medical emergency unit (AMEU), E-block wards and the department of Physiological Sciences for the support rendered during the research. Distinct recognition goes to the participants for willing giving their consent to participate in the study, without them this whole research would not have been conceivable.

**References**


APPENDICES

Appendix 1: INFORMATION FORM

PLASMA ALBUMIN LEVELS AND OUTCOME OF STROKE IN ADULT PATIENTS ADMITTED TO THE UNIVERSITY
TEACHING HOSPITAL, LUSAKA

You are invited to take part in a study looking at the plasma Albumin levels and outcome of Stroke in adult
patients admitted to UTH. This study is being done as part of requirement for a Master of Human Physiology.
Information about this study is supplied in this document. One of the study team will be on hand to explain
the contents and answer all your questions. Please make sure that you understand everything in this
document. If you decide to participate you will be asked to give consent before you take part.
Participation in this study is completely voluntary. You are under no obligation to take part. You are free to
withdraw from this study at any time. This will have no consequences for your medical care. No financial
reward will be given to any persons taking part in this study.

Title of study
Plasma Albumin Levels And Outcome Of Stroke In Adult Patients Admitted To The University Teaching
Hospital, Lusaka

Who is doing the study?
Dr Kampolo Dominic is the principal investigator under the supervision of Dr Soka Nyirenda and Dr Fastone M.
Goma. The principle investigator is responsible for the day to day running of the study. We can be contacted
via Department of Physiological Sciences, University of Zambia School of Medicine, Ridgeway Campus, Lusaka,
Zambia
Tel: +260955133730, 0977 355451
EMAIL: dkampolo@yahoo.com

What is the purpose of this study?
Stroke is a major health problem in the world and increasingly in Zambia. Cerebrovascular accident may occur
as a result of Hemorrhage or Infarction in the brain. It is an emergency and early diagnosis is important to save
life. Patients presenting with stroke can have some risk factors such as diabetes, hypertension, high
cholesterol, smoking and others may also have members of the family affected earlier on.
The aim of this project is to determine the plasma Albumin levels and outcome of Stroke and its clinical use as
a prognostic indicator in ischemic Stroke compared to hemorrhagic Stroke in adult patients.

What is Stroke?
Stroke is a sudden manifestation of a neurological deficit of vascular origin lasting more than 24 hours.

Procedure of the study
1. If you agree to take part in this project you will be asked to sign or print a consent form. You will be given a
copy of this information sheet and the consent form to keep.
2. You (patient or relatives if aphasic or unconscious) will then be interviewed. The interview will start with
questions about your age, sex and place where you live. You will then be asked questions about your illness
including the symptoms and length of time you have been unwell. You will be asked questions about your past
medical history. You will be asked a few questions related to your general health and the health of yours
parents and siblings. The interview will take about 30 minutes or less.
3. Your medical notes will be reviewed and your progress while you are an inpatient at UTH will be followed.
4. Investigations done/reviewed during this Study will include Brain Imaging(CT Scan), blood for total protein,
plasma Albumin coagulation, full blood count, Random and fasting blood glucose, Echocardiography,
Electrocardiography and Urinalysis.
The information you give in the interview and in the notes will be analyzed with the other results from the
study and will be kept strictly confidential.

Are there any risks for people taking part in this study?
Some of the questions in the interview related to your health and your family history are personal and may
cause you distress. If the interview is distressing you we will not continue.
Taking part in the interview will not interrupt your clinical care.
While we will be reviewing your notes and investigations we will not be directly involved in your clinical care, physician attending to you will be in charge of your treatment and care.

**Benefits**
The main benefit from this study will be a greater understanding of the association between plasma Albumin and outcome of Stroke in adult patients admitted to UTH. This may in future open up away for possible Albumin therapy in Stroke patients. We hope this will lead to improved care for patients with Stroke at UTH in the future.

**Confidentiality**
All information that you give in the interview and we obtain from your records will be kept confidential. Your identity will not be disclosed in any report or publication that results from this study. The data we collect will be kept securely and it will only be accessible to medical staff taking part in the research. The research ethics committees of the University of Zambia and the department of Physiological Sciences/UTH may review the data for verification purposes.

*If you have any questions about this study please ask them now. If you have any later questions or concerns please contact, Dr Kampolo Dominic at the above address. Please keep this information sheet in a safe place, thank you.*
Appendix 2: Informed consent form for plasma Albumin levels and outcome of Stroke in adults:

1. I have been invited to take part in a research project being conducted at the University Teaching Hospital by Dr Kampolo Dominic and Dr Soka Nyirenda and Dr Fastone Goma in the department of Physiological Sciences, UTH, Lusaka, Zambia; Tel:+260977355451.
2. The study is being supervised by Dr Nyirenda and Dr Goma, School of Medicine, UNZA.
3. I have been told the purposes of this research and understand the processes involved. I understand the potential distress that may occur.
4. I have been given a list of names and addresses of people and institutions I may contact in relation to this research. I have read the information on plasma Albumin levels and outcome of stroke in adult patients or have had it read or explained to me.
5. I have had the opportunity to ask questions and have had these answered satisfactorily.
6. I understand that I have the right to refuse to participate in this study or withdraw from the study at any time. I understand that refusing to take part or withdrawing from the study will in no way compromise my clinical care.
7. I agree to take part in the study

Participant’s information:

Signature (or fingerprint): ____________________________
Surname: ____________________________
Name: ____________________________
Date: ______________________

The person who conducts the informed consent discussion must also sign and date this form.

Signature: ____________________________
Surname: ____________________________
Name: ____________________________
Date: ______________________

Signature of witness, if applicable.

Witnessed by: (print name): ____________________________
Signature of Witness: ____________________________
Date: ______________________
Appendix 3. QUESTIONAIRE FOR: PLASMA ALBUMIN LEVELS AND OUTCOME OF STROKE IN ADULT PATIENTS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

A. Personal details
1. STUDY ID: ________________
2. File Number: _____________________
3. Residence (City or village name): ____________________________
4. Township of residence: ____________________________
5. Phone number of patient or next of kin___________________________
6. Age or date of birth __________________
7. Gender:   Male   Female
8. Occupation: ____________________________
9. Date of registration__________________________

B. Clinical evaluation
10. Date of onset of presenting Stroke symptoms __ __________ Time_____
   • Sudden numbness or weakness in the face-----------------------------
   • Weakness or numbness of arm, or leg, RT------------ LT------------------
   • Sudden confusion, trouble speaking, or difficulty understanding speech.---------------------
   • Sudden trouble seeing in one or both eyes, RT------------ LT------------------
   • Sudden trouble walking-------------- RT------------ LT------------------
   • Dizziness------------------
   • loss of balance, or lack of coordination-----------------
   • Sudden severe headache with no known cause-----------------------

☐ Previous history of similar symptoms -----------------------
11. Date of Admission to UTH ________________ Time
12. CT Scan Brain Done Not done Date ________Time ______
13. Date of blood draw___________________
14. Stroke Subtype----------------------------------

14. PMHx/Risks Factors:
Previous Stroke yes No
HTN Yes No
MI/CAD yes No
CHF yes No
Hyperlipidemia yes No
Diabetes Mellitus yes No
Atrial Fibrillation yes No
Valvular Heart Disease yes No
Miscarriage Yes No
Family hx of stroke: Yes No
Obesity Yes No
Smoker Current Ex>1year Never
Alcohol Current Ex>1year Never
Sickle cell disease yes No
HIV infection Yes No
CD4 Count ____________
Other

15. Medications

RTI Dyspepsia Hemoptysis
Headache/ Neckache

**Physical exam:**

17 **Vital Sign:** BP___ HR____ RR____ T______ Adm RBS_____

18 **Mental Status:**

• Alert/responsive (0)
• Arouses only to pain (2)
• Unarouseable/reflexive withdrawal (3)
• Doesn’t know age (1)
• Doesn’t know name (1)
• Doesn’t follow close/open eyes (1)
• Doesn’t follow close/open hand (1)

Sub-Total1 ____

19. **GAZE/EOMs** (Horizontal):

• Normal (0)
• Impaired (1)
• Forced (2)

20. **Visual Field**:

• Normal (0)
• Partial loss (quadrant) (1)
• Complete homonymous (2)
• Blind/bilateral (3)

21. **Facial**

• Normal (0)
• Appearance
• Minor/asymmetric/flat nasolabial fold (1)
• Lower only (2)
• Upper & lower palsy (3)

Sub-Total2 _____

22. **MOTOR**

<table>
<thead>
<tr>
<th>Motor</th>
<th>Left arm</th>
<th>Right arm</th>
<th>Left leg</th>
<th>Right leg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10sec)</td>
<td>(10sec)</td>
<td>(5 sec)</td>
<td>(5sec)</td>
</tr>
<tr>
<td>Raised extremities</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>Normal/no drift</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drift only</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some antigravity</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No effort against gravity</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No movement</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation/Joint fusion</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sub-Total arm3 + leg ____

24. **Cerebellar ataxia**: None R L
One limb (1)
Two limbs (2)
Untestable

25. **GAIT**: Normal Wide base falls to R L

26. **Sensory**:

• Normal (0)
• Impaired/unilateral (1)
• Complete loss/bilateral (2)

27. **Language**:

• Normal (0)
• Mild/moderate aphasia, but Comprehensible (1)
• Severe aphasia, almost no Communication (2)
• Global aphasia/mute (3)

28. **Dysarthria**:

• Normal (0)
• Mild/moderate slurring (1)
29. NEGLECT: □ Normal (0) □ R □ L
□ One modality (1)
□ Two modalities (2)

Sub-Total: 4

30. MODIFIED ASHWORTH SCALE TESTING
Name: __________________________________________ Date: __________
Muscle Tested Score

31. Stroke Outcome
   Admit NIHSS = Sub-Totals 1-4___________
   Admit mRankin scale ___________
   Modified Ashworth’s score_____________
   In-hospital mortality_____________________
   Discharge without Disability _______________
   Discharge with Disability ___________________

36. Date of Discharge_____________ or date of in-hospital death___________
   Date
   Time
   Name of Physician