

## **A Study on Prognostic Significance of Serum Ferritin in Patients with Acute Ischemic Stroke**

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### **I. Introduction**

As per World Health Organization, Stroke is defined as a clinical syndrome consisting of 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with duration lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin'. A transient ischemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours. The above definition do not include retinal symptoms (sudden onset of monocular loss), which should be considered as part of the definition of stroke and TIA. A non-disabling stroke is defined as a stroke with symptoms that last for more than 24 hours but later resolve, without any permanent disability. This definition includes stroke due to cerebral infarction, primary intra cerebral hemorrhage (PICH), intra ventricular hemorrhage, and subarachnoid hemorrhage (SAH); it excludes infarction caused by infection, tumor, subdural hemorrhage, and epidural haemorrhage<sup>1</sup>.

Stroke is now considered as an important health problem for all individuals and society. After Acute myocardial infarction and malignancy, Ischemic stroke is the third leading cause of death and also leading cause of hospitalization causing disability. As per Indian Council Medical Research (ICMR) reports, Stroke and Diabetes together brings the estimated national economic loss of approximately 46 billion dollars in India between 2006 to 2015. India's growth of gross domestic product (GDP) is estimated to fall by 1%. (WHO 2005). With the advent of promising therapies, Acute Ischemic stroke has a higher expectation for rapid recovery and good outcome.

The extent of brain Injury and the resultant outcome from ischemia is largely dictated at a physiological level by the severity and duration of the ischemia. The risk factors namely blood pressure (BP), smoking, diabetes, dyslipidemia, alcohol predict the happening of stroke, but still they are not completely reliable, therefore there is a continuous debate and search for prediction of occurrence of stroke and reliability of prognostic markers. In stroke have gained interest in recent years<sup>14</sup>.

In 1941, Avery and Theodore J Abernethy coined the term Acute Phase Reactants and also denoted that acutely ill patient's serum contains CRP. Acute phase reactants are the markers of inflammation and they are elevated in inflammation, infection and they tend to appear or rise in the blood whenever the immune system comes in contact with proteins. This elevation of acute phase reactants indicates inflammatory burden and it gets elevated in vascular events. Some of the acute phase reactants are

- a.  $\alpha$ 1 globulin
- b.  $\alpha$ 2 globulin
- c.  $\alpha$ 1 antitrypsin
- d. Fibrinogen
- e. Fibrinogenectin
- f. Serum Amyloid A protein
- g. Pre-Albumin
- h. Ferritin
- i. Transferrin.

Among these reactants, Pre-Albumin, Transferrin were negative phase reactants, they tend to decrease during inflammatory reactions whereas others increase during any inflammatory and infective conditions.

### **Ferritin**

Ferritin is the cellular storage protein for iron. Ferritin is essentially located within cells and constitutes the main intracellular iron storage protein (Eisenstein, 2000). The principal factor that controls cellular Ferritin content is the intracellular level of free iron (Cairo et al, 1995). Thus, Ft provides a means of storing the metal within cells in available safe manner. Ferritin is also present at a very low concentration in blood but the role of circulating Ft is still unknown. However, serum Ft has been used widely in clinical medicine chiefly as an

indicator of body iron stores<sup>4</sup>. It is an acute-phase reactant involved in cellular defense against oxidative stress and inflammation along with transferrin<sup>2</sup>.

**Functions of ferritin:**

1. Iron storage.
2. Ferroxidase activity. The heavy chain of ferritin which has ferroxidase activity, is involved in the conversion of iron from the ferrous (Fe<sup>2+</sup>) to ferric (Fe<sup>3+</sup>) forms. This limits the deleterious reaction which occurs between ferrous iron and hydrogen peroxide known as the Fenton reaction which produces the highly damaging hydroxyl radical.
3. Immune response, infection, cancer increases the serum ferritin level. Endotoxin is an positive regulator for the ferritin coding gene.
4. Stress response. The concentration of ferritin has been shown to increase in response to stresses such as anoxia.
5. Industrial applications. Ferritin is also used in materials science as a precursor in making iron nanoparticles for carbon nanotube growth by chemical vapor deposition.

**Prognostic significance of serum Ferritin in Acute Ischemic Stroke**

Recent animal experiments have suggested that iron overload contributes to the development of vascular diseases by promoting thrombosis after arterial injury (Day *et al*, 2003). High serum Ft on admission of acute stroke patients (within 24 to 48 h after stroke onset) was reported to predict a bad prognosis implicating that increase in body iron stores before stroke onset can aggravate the cytotoxicity of brain ischemia. . Now it has been suggested that it influences the prognosis of Ischemic stroke and also acts as a risk factor for Ischemic episodes by enhancing atherogenesis<sup>3</sup>.

**Aims And Objective**

- 1) To analyze the prognostic significance of serum ferritin with severity of Stroke in correlation with stroke scales (NIHSS and MRS).
- 2) To study the relationship between serum ferritin and various risk factors for stroke.

**II. Materilas And Methods**

**Study population:**

60 Acute ischemic stroke patients admitted in medical wards of Government Vellore medical college and Hospital.

**Study design:**

Cross sectional (Prospective) observation study

**Period of study:**

March 2016 to October 2016

**Definitions followed in this study:**

**Stroke:**

As per WHO criteria, Acute Stroke is defined as “rapidly developing focal or generalized (for coma patients) neurological alterations in cerebral function with signs and symptoms lasting for more than 24 hours or leading on to death, without any apparent cause for stroke except vascular etiology.

**Hypertension:**

Hypertension was defined as patients with previous record of at least 2 recordings of >140 / 90 mmHg or patients who are on regular intake of anti hypertensive medications.

**Diabetes:**

Diabetes was defined as patients with Random Blood Sugar of >200mg/dL, Fasting blood sugar of >126 mg/dL, Post prandial blood sugar of >200mg/dL or patients who are in need of regular intake of anti-diabetic drugs.

**Dyslipidemia**

Dyslipidemia is defined as patient’s with fasting cholesterol values of more than 220mgs/dl.

### **Nihss Score**

NIHSS was developed to assess the impairment caused by a stroke. NIHSS is composed of 11 components, each of which scores a specific ability between a 0 and 4. A score of 0 indicates normal function, while a higher score is indicative of impairment.<sup>[1]</sup> Total scores range from 0-42 with higher values representing more severe infarcts.

1. Cranial Nerve/ Visual disturbances
2. Level of Consciousness
3. Motor weakness

4. Language/ Neglect – were the four important areas to be taken into account. Even based on this clinical parameter, scores can be computed and severity can be assessed.

### **Merits Of Nihss**

- a. Helps in diagnosing Cerebrovascular accidents.
- b. To know the prognosis of stroke
- c. To determine functional disability
- d. Rapid way of assessing the patient which can be done in 10 mins.

### **Interpretation of NIHSS Score**

0 – No stroke

1-4 – Minor stroke

5-15 – Moderate stroke

16-20 – Moderate to severe stroke

21-41 – Severe stroke

In this study, patients with a score of 1- 4 were considered as MILD, score 5-15 were considered as MODERATE, score >15 were considered as SEVERE category.

### **MRS score**

**Parameters:** MRS carries a total score of 0-6.

Score 0 = Patient should not have any symptoms at all

Score 1 = Patient should not have any significant disability in spite of presence of symptoms and can able to perform routine daily normal activities.

Score 2 = Patient will have slight disability and the person cannot perform all routine activities but manages to do his personal work without help.

Score 3 = Patient is having moderate disability and needs some help, but able to walk without assistance.

Score 4 = Patient will have moderately severe disability and cannot walk without help and unable to do his personal affairs without assistance

Score 5 = Here patient is having severe disability and the affected individual is bedridden, urinary incontinence will be present and needs continuous nursing care and attention.

Score 6 = Dead.

MRS score of 3,4,5,6 were included under Good Outcome and scores of 1,2 were considered as Poor outcome.

### **Inclusion criteria:**

1. All patients with new onset focal neurological deficit following ischemic stroke, presented within 48 hours of onset of stroke are taken into study.
2. Patients >14 years and of both sexes are included in the study.
3. Patients with new onset stroke with past history of hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol were included.

### **Exclusion criteria:**

1. Patients with age more than 80 years were excluded.
2. Patients with malignancy and clinical findings and blood investigations suggestive of infection were excluded.
3. Individuals with Connective Tissue disorders and Rheumatic heart disease, Coronary artery diseases were excluded.
4. Patients with prior history of transient ischemic attacks or reversible Ischemic neurological deficit, cerebrovascular accidents were excluded
5. Patients with features of hemorrhage such as sub-dural hemorrhage, sub-arachnoid hemorrhage, and intracerebral hemorrhage were excluded with the aid of CT scan.

- 6. History of recent surgery and trauma.
- 7. CNS tumors.

### III. Study Methods

60 patients who had acute ischemic stroke were included for study. Those patients who got admitted within 24 hours of stroke onset only were taken for study. As soon as patient got admitted, verbal consent was obtained from patient or attenders. Then complete relevant medical history, neurological examination, routine blood and CT scan were done and all data were recorded in a standardized proforma.

CT scan was taken to exclude the hemorrhagic stroke. Serum ferritin was taken as soon as patient got admitted in the hospital. National Institute of Health Stroke Scale (NIHSS) scoring was applied at the time of admission and these patients were grouped into mild, moderate and severe category.

These Acute Ischemic Stroke patients were treated according to standard treatment protocols. None of the patients in the study group were thrombolysed. Anti edema measures were adopted with either intravenous Mannitol or oral Glycerol. Modified Rankin Scale was applied to know the functional recovery of the patient after 4 weeks when patient is on follow up and attending the review op.

### IV. Statistical Methods

All the collected data were computed in master chart. Statistical data analysis was done. Chi Square test, Mean, Standard deviation, 'p' values were calculated. A 'p' value less than 0.05 denotes significant relationship. Pearson's r correlation test and scatter plot analysis were also done for given data.

### V. Results And Analysis

Sex distribution: among the 60 stroke patients included in our study, majority were males n=38 (63.33%).

#### Sex vs serum Ferritin

Out of 38 male patients, number of male patients who had normal serum ferritin are 16 (42.11 %) and the number of male patients who had high serum ferritin 22 (57.89 %). And out of 22 female patients, 9 (40.91 %) female cases had normal serum Ferritin and 13 (61.9 %) female patients had high serum Ferritin level. There was no statistical significance between the serum ferritin levels among males and females p value = 0.927

#### Age Distribution

Out of 60 patients, 14(23.33%) patients were in the age group of ≤ 50 years and 46 (76.67%) patients were in the age group of ≥ 50 years.

#### Age Vs Serum Ferritin

Out of 14 (23.33% ) patients who were in the age group of ≤ 50 years, 6 (42.86% ) patients had normal serum ferritin and 8 (57.14% )patients had high serum ferritin. Out of 46 (76.67%) patients who were in the age group of ≥ 50 years, 19 (41.30%) patients had normal serum ferritin and 27 ( 58.70% ) patients had high serum ferritin .

There was no significant difference in ferritin levels between the two age groups. P value 0.918

#### Smokers Vs Serum Ferritin

Serum ferritin profile was done in all 60 cases which includes both smokers and non smokers .Out of 27 patients who are smokers , 14 (51.85% ) patients had normal serum ferritin and 1 ( 57.1% ) patients had high serum ferritin . Out of 33 patients, who are non smokers, 11(33.33 % ) patients had normal serum ferritin and 22 ( 66.67 % ) patients had high serum ferritin. The correlation between smoking and serum ferritin was statistically insignificant p value 0.236

#### Diabetics Vs Serum Ferritin

Serum ferritin values were correlated with both diabetics and non diabetics patients. Among 16 non diabetics, 11 (68.75%) patients had normal serum ferritin and 5 (31.25%) patients had high serum ferritin. Among 44 diabetics, the number of patients with normal serum ferritin were 14 (68.75%) and with high serum ferritin were 30 (66.7%).

| Diabetes | No. Of Patients | Total  |      |  |
|----------|-----------------|--------|------|--|
|          |                 | Normal | High |  |

|       |       |        |        |      |
|-------|-------|--------|--------|------|
|       | Count | 14     | 30     | 44   |
| Yes   | %     | 31.82% | 68.18% | 100  |
|       | Count | 11     | 5      | 16   |
| No    | %     | 68.75% | 31.25% | 100  |
| Total | Count | 25     | 35     | 60   |
|       | %     | 41.67% | 58.33% | 100% |

The correlation between serum ferritin and Diabetes was significant statistically.

### Hypertension Vs Serum Ferritin

Serum ferritin values were correlated in both hypertensive and non hypertensive patients. Out of 21 non hypertensive patients, 13 (61.90%) patients had normal serum ferritin and 8 (38.10%) patients had high serum ferritin. Out of 39 hypertensive patients, 12 (30.77%) patients had normal serum ferritin and 27 (69.23%) patients had high serum ferritin.

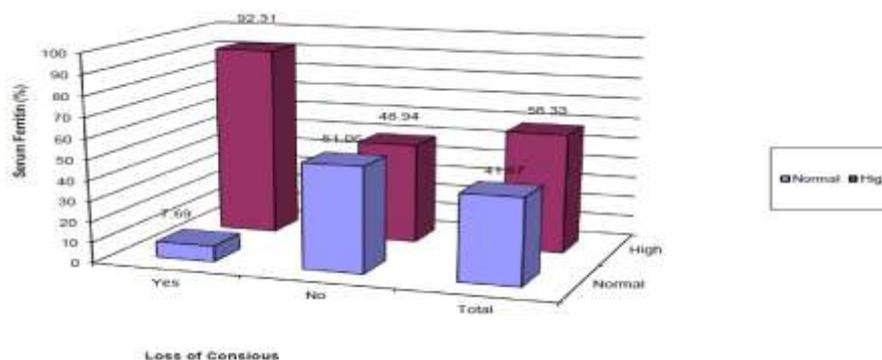
| Hypertension       | No. Of Patients | Total  |        |      |
|--------------------|-----------------|--------|--------|------|
|                    |                 | Normal | High   |      |
| Yes                | Count           | 12     | 27     | 39   |
|                    | %               | 30.77% | 69.23% | 100% |
| No                 | Count           | 13     | 8      | 21   |
|                    | %               | 61.90% | 38.10% | 100% |
| Total              | Count           | 25     | 35     | 60   |
|                    | %               | 41.67% | 58.33% | 100% |
| <b>Significant</b> |                 |        |        |      |

The correlation between serum ferritin and hypertension was statistically significant

### Loss Of Consciousness Vs Serum Ferritin

In Patients with loss of consciousness, serum ferritin profile was done. The number of patients with normal serum ferritin were 24 (51.06%) and high serum ferritin were 15 (48.94%) among conscious patients. The number of patients with normal serum ferritin were 1 (7.69%) and high serum ferritin were 13 (92.31%) among un-conscious patients.

The correlation between serum ferritin and unconscious patients was statistically significant with p value of 0.013



### Descriptive Statistics

The maximum and minimum mean values of serum ferritin in the study are 462.12 and 26.48 with an average mean of 241.39.

The maximum and minimum mean values for NIHSS scoring system in the study is 23 and 5 with an average mean of 14.42

The maximum and minimum mean values for MRS scoring system in the study is 6 and 1, with an average mean of 3.42.

**From this, it is evident that patients with a minimum serum ferritin mean value of 26.48 had**

- NIHSS score minimum mean value of 5 which comes under moderate group
- MRS minimum mean value of 1 which comes under good outcome.

**And patients with serum ferritin maximum mean value of 462.12 had**

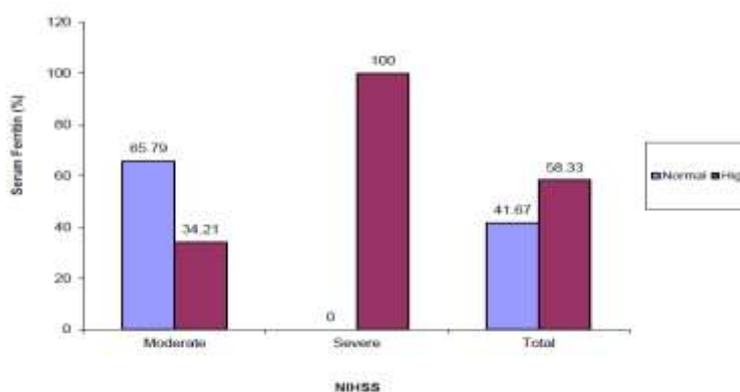
- NIHSS maximum mean value of 23 which comes under severe category
- MRS maximum mean value of 6 which comes under poor outcome.

**Table: Descriptive Statistics**

| Variables      | No. | Minimum | Maximum | Mean   | Std. Deviation |
|----------------|-----|---------|---------|--------|----------------|
| Serum Ferritin | 60  | 26.48   | 462.12  | 241.39 | 120.16         |
| Nihss.Score    | 60  | 5       | 23      | 14.42  | 6.31           |
| Mrs.Score      | 60  | 1       | 6       | 3.42   | 1.44           |

**Serum Ferritin Vs Nihss**

Serum ferritin profile was done in all patients and it was summated with various scoring categories of NIHSS. Out of 38 cases who comes under moderate category in NIHSS , 25 ( 65.79% ) cases had normal serum ferritin values and 13 ( 34.21% ) cases had high serum ferritin . Out of 22 cases who were under severe category , all the 22 (100%) cases had high serum ferritin .



**Pearson’s R Correlation And Scatter Plot Analysis**

This table denotes strong correlation between serum ferritin and NIHSS score. Change in serum ferritin values strongly correlates with change in NIHSS scores. There is also positive correlation between NIHSS score and serum ferritin, that is any increase in serum ferritin will increase NIHSS scores and decrease in serum ferritin values will decrease NIHSS scores.

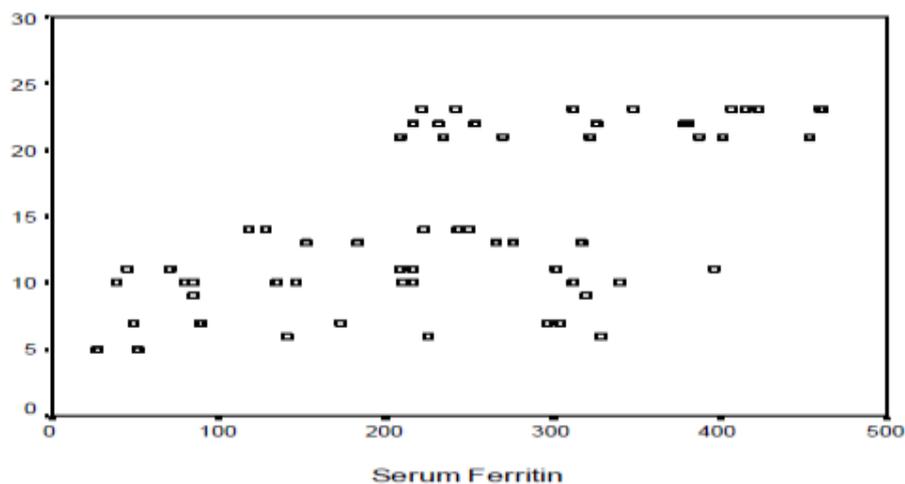
**Table: Serum Ferritin Vs Nihss**

|                |                     | Serum ferritin | NIHSS        |
|----------------|---------------------|----------------|--------------|
|                | PEARSON CORRELATION | 1              | 0.613        |
| Serum ferritin | P VALUE             |                | <b>0.000</b> |
|                | N                   | 60             | 60           |
|                | PEARSON CORRELATION | 0.613          | 1            |
| NIHSS          | P VALUE             | 0.000          |              |
|                | N                   | 60             | 60           |

There was a statistically significant correlation between the serum ferritin levels and the NIHSS scoring scale.

**Pearson’s R Correlation And Scatter Plot Analysis**

Scatterplot analysis reveals that there is a positive correlation between serum ferritin values and NIHSS scores. Increase in serum ferritin increases with NIHSS scores.



**Serum Ferritin Vs Modified Rankin Scale**

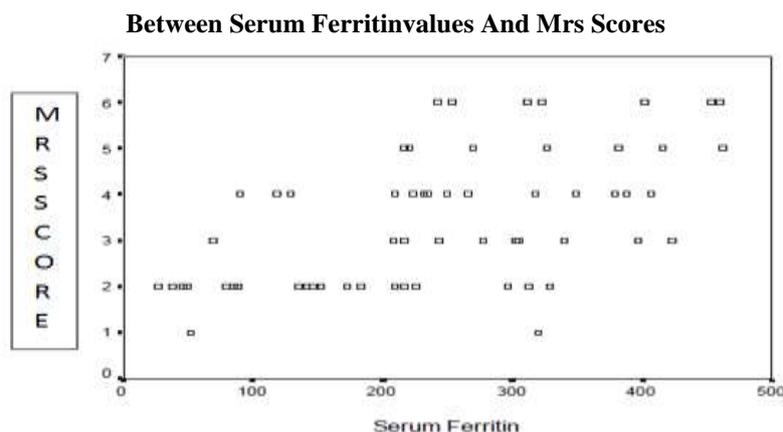
Serum ferritin values were correlated with various outcomes in Modified Rankin Scale. Among 22 good outcome patients, 17 (72.27%) cases had normal serum ferritin values and 5 ( 27.23% ) cases had high serum ferritin . Among 38 poor outcome patients, 8 (21.05%) cases had normal serum ferritin and 30 (78.95%) cases had high serum ferritin.

**Pearson’s R Correlation And Scatter Plot Analysis**

This table denotes strong correlation between serum ferritin and MRS score. Change in serum ferritin values strongly correlates with change in MRS scores. There is also positive correlation between MRS score and serum ferritin values, that is any increase in serum ferritin will increase MRS score and decrease in serum ferritin values will decrease MRS score

| TABLE 19 serum ferritin VS Modified Rankins Scale |                     |                |              |
|---|---------------------|----------------|--------------|
|   |                     | Serum ferritin | MRS          |
| Serum ferritin                                    | PEARSON CORRELATION | 1              | 0.560        |
|   | P VALUE             |                | <b>0.000</b> |
|   | N                   | 60             | 60           |
| MRS   | PEARSON CORRELATION | 0.560          | 1            |
|   | P VALUE             | <b>0.000</b>   |              |
|   | N                   |                |              |

**Pearson’s R Correlation And Scatter Plot Analysis**



## VI. Discussion

is now considered as a major consequence of cerebrovascular accidents and health hazard to the society. In this study of prognostic significance of serum ferritin in Acute Ischemic Stroke consists of a group of 60 patients who were admitted in Government Vellore medical college & Hospital, from March 2016 to October 2016. In this study, serum ferritin was taken within 48 hrs and NIHSS scoring was applied on the day of admission.

Totally 60 cases were included in the study. Among the 60 cases included in this study cases 35(58.33%) had high serum ferritin values [ $\geq 300$  mg/l (male) ,  $\geq 200$  mg/ml (female) ] and 25 cases (41.67%) had normal serum ferritin [ $\leq 300$  mg/l (male) ,  $\leq 200$  mg/ml (female) ].

Number of patients died in this group is 7. All these patients had a high serum ferritin. Out of these 35 cases who has high serum ferritin , 37.14% of cases comes under moderate category and 62.86% cases comes under severe category. On the other hand, among the remaining 25 cases who had normal serum ferritin , all the 22 cases come under moderate group and none in severe group.

Pearson's r correlation also reveals positive correlation between serum ferritin and NIHSS scores. Pearson's r value is 0.613 . A positive correlation exists between these 2 variables with a statistically significant 'p' value . Scatter plot analysis reveals the positive correlation between serum ferritin & NIHSS. Any increase or decrease in serum ferritin score analogous linearly with increase/decrease severity score of NIHSS.

Out of 35 cases with high serum ferritin , 5 cases were in good outcome category and 30 cases in poor outcome category of MRS scores.

In contrast among 25 cases with normal serum ferritin , 17 cases were in good outcome and 8 cases were in poor outcome category in MRS Score. Pearson's r correlation analysis reveals positive correlation between serum ferritin and MRS. Pearson's r value is 0.560 and is positive variable. Increase in serum ferritin will favour the poor outcome of patients in terms of death and severe disability.

### Sex

In the present study, Incidence of stroke patient in male is 63.33% whereas in female patients it is 36.67%. This incidence data was supported by Thomas Kuruvillet al.<sup>35</sup> in which males has higher incidence than female . No significant relationship exists between serum ferritin and sex in our present study. This result is against the finding of Zacharski et al. The small sample value (only 60 cases considered) may be the reason for this contradiction.

### Age

In the present study, incidence of stroke is more common among patient with the age group of more than 50 years. There is no significant correlation between serum ferritin and age . This was supported by JHematolet al<sup>11</sup>.

### Smoking

In this present study, there is no significant correlation between serum ferritin and smoking with a p-value of 0.236. This was supported by study Salonen JT al<sup>12</sup>.

### Diabetes

this present study, there is significant correlation between Serum Ferritin and diabetes with a p-value of 0.023. This was supported by number of studies.

**Studies in favor of rise in blood sugar increases Serum Ferritin level**

| S.No | Study                        | Year |
|------|------------------------------|------|
| 1.   | Fernandez et al <sup>5</sup> | 2002 |
| 2.   | Thomas MC et al <sup>6</sup> | 2004 |
| 3.   | Kim NH et al <sup>7</sup>    | 2000 |
| 4.   | Eshed I et al <sup>8</sup>   | 2001 |

**Hypertension**

In this present study, there is a significant correlation between Serum Ferritin and Hypertension with a p value of 0.040 . These findings are in agreement with following studies.

| S.No | Study                         | Year |
|------|-------------------------------|------|
| 1.   | Wrede et al <sup>9</sup>      | 2002 |
| 2.   | Piperno A et al <sup>10</sup> | 2002 |

**Ferritin and out come**

This study demonstrates the prognostic significance of serum ferritin in acute ischemic stroke patients in correlation with stroke scores, which were measured at the time of admission (NIHSS) and four weeks after discharge. (MRS).In our study concludes that raised Serum Ferritin is associated with poor prognosis. There are other studies favoring this fact.

**Studies favoring Prognostic Significance of serum ferritin in Acute Ischemic Stroke**

| S.No | Studies                                | Year |
|------|--|------|
| 1.   | Daphne L et al <sup>4</sup>            | 2005 |
| 2.   | Davalos A et al <sup>3</sup>           | 2000 |
| 3.   | Fernandez – Real JM et al <sup>5</sup> | 1994 |
| 4.   | Erdemoglu AK et al <sup>13</sup>       | 2002 |

**VII. Conclusion**

- a. This present study is a cross sectional observation study of prognostic significance of serum ferritin in acute ischemic stroke patients.
- b. The present study shows male predominance with majority of patients in the age group of greater than 50 years.
- c. The present study revealed significant association between serum ferritin and diabetes mellitus & hypertension.
- d. This study demonstrates the significant rise in serum ferritin in ischemic stroke patients in correlation with high scores with NIHSS which indicates the severity.
- e. This study reveals the poor outcome in correlation with high serum ferritin values and good outcome in correlation with low serum ferritin values. .
- f. There is no statistically significant relationship between serum ferritin and age, sex and smoking.

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