

# Serum Level of Ferritin and Fibrinogen as Prognostic Indicator for Acute Ischemic Stroke

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**Abstract:**

**Background:** Stroke is the main cause of disability worldwide, the second common cause of dementia and the second main cause of death after ischemic heart diseases. Acute phase response proteins i.e. ferritin, fibrinogen and others play an important role in the pathogenesis of ischemic stroke because acute cerebral ischemia triggers interleukin-6 release into cerebrospinal fluid and blood, which is a key mediator of acute phase reaction and induces synthesis of acute phase proteins during ischemia. **Aim:** This study aims to explore the correlation between serum ferritin and plasma fibrinogen levels and the neurological disability of acute ischemic stroke. **Methods:** This study was carried out in the Department of Neurology, Benha University from December 2019 to January 2021 to compare serum ferritin and plasma fibrinogen levels between a group of fifty stroke patients and fifty control, then to correlate their levels with clinical outcome in patients **Results:** Our study revealed that means of serum ferritin and plasma fibrinogen levels were 143.17 ng/ml and 2.61 mg/ml in patients, while in control they were 78.36 ng/ml and 2.0 mg/ml respectively. We also found that high levels of ferritin and fibrinogen among cases were associated with poor outcome, as clarified by GCS and NIHSS scores and by infarct volume. **Conclusion:** It may be concluded that serum ferritin and plasma fibrinogen are significantly higher in AIS patients, and their elevated levels are associated with early neurological deterioration.

**Key words:** Ferritin, Fibrinogen, Stroke.

**List of Abbreviations:** AIS (acute ischemic stroke)

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## Introduction

Stroke is a disorder characterized by rapidly developing clinical manifestations of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. This definition includes cerebral infarction (ischemic stroke), non-traumatic intracerebral hemorrhage, intraventricular hemorrhage and most cases of subarachnoid hemorrhage [1].

It is assumed that the acute phase response proteins i.e. ferritin, fibrinogen and others play an important role in the pathogenesis of ischemic stroke because acute cerebral ischemia triggers interleukin-6 release into cerebrospinal fluid and blood, which is a key mediator of acute phase reaction and induces synthesis of acute phase proteins during ischemia [2].

Serum ferritin is a suitable index of the amount of cellular iron stores and consequently might be related to the availability of iron in the infarcted area. In brain tissue most of the non-heme iron is in the form of ferritin, which is localized in astrocytes and microglia. It is an acute phase response protein and its concentrations

increases during inflammation [3].

The role of iron overload in stroke is poorly documented. However, high serum Ferritin on admission of acute stroke patients (within 24 to 48 h after stroke onset) was reported to predict a bad prognosis [4, 5 and 6].

Serum ferritin has gained a great clinical interest in recent times, and is now under research as an important prognostic indicator of stroke. This has also enhanced research in the therapeutic role of iron chelation in improving stroke prognosis [7, 8 and 9].

Fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. It is a high molecular weight plasma adhesion protein and a biomarker of inflammation. Increased levels of fibrinogen result in changes in blood rheological properties that exacerbate the complications in peripheral blood circulation during stroke [10 and 11].

Several studies showed that elevated plasma fibrinogen level is associated with worse functional outcome after stroke [12, 13, 14 and 15].

### **Aim of Work:**

This study aims to explore the correlation between serum ferritin and plasma fibrinogen levels and the neurological disability of acute ischemic stroke.

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### **Subjects and methods:**

This study is a combined study; case control then prospective study.

It was conducted during the period from December 2019 to January 2021 upon 50 patients and 50 controls. The patients were recruited from Benha University Hospital. The control group was chosen to be age and sex matched and apparently healthy.

This study gained the approval of ethical committee and the verbal consents of the patients.

Inclusion Criteria were; acute ischemic cerebral infarction confirmed by CT scan, age ranges from 18-80 years, both sexes were included; patients presented within 48 hours from onset, patients who agreed to join the study according to the ethical considerations.

Exclusion Criteria were; hemorrhage revealed by CT scan, infection and inflammation, malignancy, anemia, age

below 18 years or above 80 years, patients with chronic kidney disease or liver cell failure.

All patients were subjected to; thorough medical and neurological examination, routine laboratory investigations including CBC, liver and kidney function tests, Serum ferritin and plasma fibrinogen levels measured within 48 hours from onset of symptoms and assessed by ELISA (Enzyme-linked Immunosorbent Assay), CT scan on brain, infarct volume measurement using ABC/2 method, Disability assessment on admission and after one week using: NIHSS, MRS, GCS. Data was analyzed with the help of SPSS version 26.

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### **Results:**

#### **Table (1): Comparison between case and control groups**

It showed that when comparing Case and Control groups there were:

- No statistically significant difference regarding age and sex distribution (**P >0.05**).
- While serum ferritin and plasma fibrinogen showed a high statistically significant positive correlation (**p< 0.01**).

**Table (2): Ferritin level and cases prognosis according to different scores**

- We divided stroke patients according to serum ferritin into two groups (normal ferritin group/ elevated ferritin group).
1. By measuring GCS on admission and after one week; we found that only (4.3%) of cases worsened in the normal ferritin group, while (50%) of cases worsened in the high ferritin group according to GCS ( $p < 0.05$ ).
  2. By measuring NIHSS on admission and after one week; we found that only (4.3%) of cases worsened in the normal ferritin group, while (50%) of cases worsened in the high ferritin group according to NIHSS ( $p < 0.05$ ).
  3. By measuring MRS on admission and after one week; we found that (2.2%) of cases worsened in the normal ferritin group, while (0%) of cases worsened in the high ferritin group according to MRS ( $P > 0.05$ ).

**Table (3): Infarct volume in relation to serum ferritin**

- The patients with elevated serum ferritin showed a larger infarct volume with a mean of 34 cc, compared to patients with normal ferritin where the mean was 17.22 cc, ( $p < 0.01$ ).

**Table (4): Fibrinogen level and cases prognosis according to different scores**

- We divided stroke patients according to plasma fibrinogen into two groups (normal fibrinogen group/ elevated fibrinogen group).
1. By measuring GCS on admission and after one week; we found that only (4.3%) of cases worsened in the normal fibrinogen group, while (50%) of cases worsened in the high fibrinogen group according to GCS ( $p < 0.05$ ).
  2. By measuring NIHSS on admission and after one week; we found that only (4.3%) of cases worsened in the normal fibrinogen group, while (50%) of cases worsened in the high fibrinogen group according to NIHSS ( $p < 0.05$ ).
  3. By measuring MRS on admission and after one week; we found that (0%) of cases worsened in the normal fibrinogen group, while (25%) of cases worsened in the high fibrinogen group according to MRS ( $P > 0.05$ ).

**Table (5): Infarct volume in relation to plasma fibrinogen**

- The patients with elevated plasma fibrinogen level showed a larger infarct volume with a mean of 33.5 cc, compared to patients with normal

fibrinogen where the mean was 17.26 cc, with a high significant positive correlation (**p< 0.01**).

**Table (1):** Comparison between case and control groups

	Case group (50)		Control group (50)		Statistical test (x2)	P value
	No	%	No	%		
<b>Sex</b>						
Male	32	64.0	31	62.0	0.04	0.84
Female	18	36.0	19	38.0		
<b>Age (yrs)</b> mean ±SD	61.74±10.01		60.48±8.00		St t= 0.70	0.76
<b>S. ferritin (ng/ml)</b> mean ±SD	143.17±72.31		78.36±18.96		St t=6.13	<0.001**
<b>P. fibrinogen (mg/dL)</b> mean ±SD	2.61±1.07		2.0±0.33		St t=3.87	<0.001**

**Table (2):** Ferritin level and cases prognosis according to different scores

	S ferritin ≤250 (46)		S ferritin >250 (4)		Statistical test (FET)	P value
	No	%	No	%		
<b>Score changes after 1w</b>						
<b>GCS changes</b> n(%)						
Worsened	2	4.3	2	50	6.51	0.034*
Improved	12	26.1	0	0.0		
No change	32	69.6	2	50		
<b>NIHSS changes</b> n(%)						
Worsened	2	4.3	2	50	6.35	0.049*
Improved	37	80.5	2	50		
No change	7	15.2	0	0.0		
<b>MRS changes</b> n(%)						
Worsened	1	2.2	0	0.0	1.12	1.0
Improved	24	52.2	2	50		
No change	21	45.6	2	50		

**Table (3):** Infarct volume in relation to serum ferritin

	S ferritin ≤250 (46)	S ferritin >250 (4)	Statistical test (St t)	P value
<b>Infarct Volume (cc)</b> Mean ±SD	17.22±9.32	34±2.83	8.51	<0.001**

**Table (4):** Fibrinogen level and cases prognosis according to different scores

	P fibrinogen <4.5 (mg/dL) (46)		P fibrinogen >4.5 (mg/dL) (4)		Statistical test (FET)	P value
	No	%	No	%		
<b>Score changes after 1w</b>						
<b>GCS changes n(%)</b>						
Worsened	2	4.3	2	50.0	FET=	0.034*
Improved	12	26.1	0	0.0	6.51	
No change	32	69.6	2	50.0		
<b>NIHSS changes n(%)</b>						
Worsened	2	4.3	2	50.0	FET=	0.012*
Improved	39	84.8	0	0.0	8.84	
No change	5	10.9	2	50.0		
<b>MRS changes n(%)</b>						
Worsened	0	0.0	1	25.0	FET=	0.14
Improved	26	56.5	0	0.0	3.96	
No change	20	43.5	3	75.0		

**Table (5):** Infarct volume in relation to plasma fibrinogen

	P fibrinogen <4.5 (46)	P fibrinogen >4.5 (4)	Statistical test (St t)	P value
<b>Infarct Volume (cc)</b> Mean ±SD	17.26±9.42	33.5±0.71	11.33	<0.001**

## Discussion:

In the present study, we found that the serum ferritin level was high in patients with acute ischemic stroke and ranged from 46.8 to 287.7ng/ml with a mean of 143.17 (S.D ± 72.31), while ferritin level in the healthy control group ranged from 40 to 110ng/ml with a mean of 78.36 (S.D ± 18.96). We also found that the plasma fibrinogen level was high in patients with acute ischemic stroke and ranged from 1.55 to 5.56mg/ml with a mean of 2.61 (S.D ± 1.07), while fibrinogen in controls ranged from 1.55 to 2.60 mg/dL

with a mean of 2.0 (S.D ± 0.33) with a high statistically significant positive correlation ( $p < 0.01$ ). These results in agreement with previous studies which showed that serum ferritin and plasma fibrinogen levels were 83.1 ng/ml and 190.6 mg/dl in subjects with acute ischemic stroke, while in control subjects were 41.3 ng/ml and 177.0 mg/dl respectively [16].

Our study also found a statistically significant positive correlation ( $p < 0.05$ )

regarding serum ferritin level and changes in GCS and NIHSS scores (where these changes reflect the prognosis in term of improvement, worsening or no change). In cases with normal ferritin levels; GCS showed that (4.3%) worsened after 1 week compared to cases with high ferritin level where (50%) worsened. In cases with normal ferritin; NIHSS showed that (4.3%) worsened after 1 week compared to cases with high ferritin level where (50%) worsened. We also found a statistically significant positive correlation ( $p < 0.05$ ) regarding the plasma fibrinogen level and changes in GCS and NIHSS scores. In cases with normal fibrinogen levels; GCS showed that (4.3%) worsened after 1 week compared to cases with high fibrinogen level where (50%) worsened. In cases with normal fibrinogen; NIHSS showed that (4.3%) worsened after 1 week compared to cases with high fibrinogen where (50%) worsened.

These results in agreement with previous study which showed that high ferritin level was associated with poor outcome in stroke patients, disability was measured within 48 hours of stroke onset and on day six [17], the study which found that the serum ferritin has direct correlation with worse prognosis in patients of stroke. The mean level of serum ferritin in the

group of clinically improved (87.01) was much lesser compared to the group clinically deteriorated or died (458.7) among patients of ischemic stroke [18], the study which observed positive correlation between serum ferritin and NIHSS scores ( $P = 0.000$ ) [19], the study which also revealed that there was a significant correlation between the values of serum ferritin and NIHSS ( $P < 0.001$ ) and modified Rankin score ( $P < 0.001$ ) [20], the study which suggested that fibrinogen can be involved as a risk factor for acute ischemic stroke and its prognosis [21], the scientists who found that the baseline fibrinogen level  $\geq 450$ mg/dL was significantly associated with poor functional outcome at 90 days even taking into account the covariates of age and pretreatment stroke severity [12 and 22], the study which evaluated fibrinogen levels in 200 patients with acute carotid artery distribution ischemic strokes who were treated with intravenous rtPA. They found that patients with fibrinogen levels  $>360$  mg/dL had poorer outcomes on discharge based on (NIHSS) scores and higher three-month mortality [23].

In contrast to our results, this study showed that the determination of ferritin level in CSF had no practical value in the evaluation of patients with meningeal

reaction and cerebrovascular events [24], another study founded no association with either univariate or multivariate analyses between mortality at 1 year and fibrinogen levels obtained within 12 hours of symptom onset in a mixed group of hospitalized patients with cerebrovascular disease [25].

Serum ferritin and plasma fibrinogen also has a high statistically significant positive correlation ( $p < 0.01$ ) with the volume of infarction, this is in agreement with the study which showed a significant correlation between the infarct volume and fibrinogen levels ( $r$  coefficient = 0.61;  $p < 0.05$ ) [26].

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### Conclusion:

According to these data, we suggest that serum ferritin and plasma fibrinogen levels are powerful predictors of vascular events. Their elevated levels are associated with increased risk of stroke.

There is an association between serum ferritin and plasma fibrinogen elevated levels and stroke prognosis, where the elevated levels were found to be predictive of poor outcome.

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