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## Original Research Article

## A study of association of serum ferritin as a prognostic marker in acute cerebrovascular accident

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## ABSTRACT

**Introduction:** Cerebrovascular disease (CVD) is the third leading cause of death in developed countries and is now emerging as the commonest preventable life-threatening neurological problem worldwide. It makes an important contribution to morbidity and mortality in developed as well as developing countries. The prognosis of acute stroke is determined by a series of factors some of which may be used in the early stages of stroke to predict prognosis and mortality. However, the role of inflammatory markers in predicting functional outcome in stroke remains controversial, Iron and ferritin are known to have an important role in stroke as well as in other disorders. Serum ferritin which is considered as an acute phase reactant has also been used for assessing the severity and prognosis of stroke. Therefore, testing of serum ferritin is useful in identifying high risk patients.

**Aims:** 1: To study the effect of level of serum ferritin with early neurological deterioration and the outcome in patients of acute stroke. 2: Association of serum ferritin in ischemic and haemorrhagic stroke.

**Materials and Methods:** 50 patients with acute stroke were selected based on inclusion and exclusion criteria. Appropriate questionnaire was used to collect the data of patients. Diagnosis of stroke was confirmed by CT or MRI scan of brain and examination was done by Canadian stroke scale at the time of admission. About 5ml of venous blood Sample from cubital vein was collected for measuring serum ferritin levels, it was performed within 48hrs of onset of symptoms by using CLIA method. Neurological assessment was repeated on the day of discharge to assess the clinical improvement and prognosis of the stroke patients.

**Results:** Totally 50 patients of acute stroke were included in our study, majority of the patients are males 35 (70%), and females are 15(30%). Approximately 36% were in the age group of 51-60 years. In this study ischemic stroke was seen in 45 (90%) of the patients and 5 (10%) had hemorrhagic stroke. The serum ferritin levels are normal in 41(82%) and high in 9(18%) of the patients. Canadian stroke scale interpretation on the day of discharge showed 20% of the patient are deteriorated, 66% are in the same status and 14% of the patients are improved clinically. The patients with haemorrhagic stroke had high serum ferritin level 60.0% and ischemic stroke are 13.3%. Those patients with high serum ferritin levels had higher deterioration in Canadian stroke scale ( $p < 0.001$ ). The mean serum ferritin levels are higher in deteriorated patients 199.29% when compared to other status group in Canadian stroke scale.

**Conclusion:** High levels of serum ferritin correlates well with early neurological deterioration of stroke patients. Based on this study finding, that high serum ferritin level within 48 hours after the onset of symptoms of stroke helps to predict the early prognosis. Therefore, testing of serum ferritin is useful in identifying high risk patients.

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## 1. Introduction

Stroke is an emerging important health problem in our society. Ischemic stroke is the third major cause of death, causes more hospitalization with disability. With the occurrences of newer therapies, acute ischemic stroke has a higher hope for quick recovery and better outcome. Despite novel therapies, poor prognosis may still happen because ischemic stroke is a heterogeneous disease in which result is influenced by several factors. The risk factors specifically blood pressure (BP), alcohol, diabetes mellitus, dyslipidaemia and smoking predict the occurrences of stroke. Outcome is further influenced by genetic predisposition, temperature, glucose and other unknown factors but still they are not completely responsible, therefore there is a continuous dispute and search for prediction of occurrence of stroke and reliability of prognostic markers in stroke have acquired interest in current years.

Inflammatory process plays an important role in pathophysiology of stroke. There is a production of proteins called acute Phase Proteins, when the individual is exposed to any insult such as infection and injury. This acute phase protein (APP) is elevated in both acute and chronic inflammatory states. The acute phase reactants are fibrinogen, ferritin, haptoglobin, hsCRP, Complements (C3), Complements (C4) and tumour necrosis factor (TNF).

Many studies shown that iron plays a major role in neurotoxicity and oedema formation after stroke. Ferritin is a major cellular iron storage protein. In brain tissue most of the non-heme iron is in the form of ferritin which is located in astrocytes and microglia. In cerebrovascular disease the oxygen free radicals increase the volume of iron in the cytosol during oxidative stress by enabling the release of iron from ferritin. Ferrous iron mediated free radical mechanisms assumed to play a major role in acute stroke. Ferritin is also considered as an acute phase reactant. Therefore, elevation of acute phase reactant indicate inflammatory burden and it gets elevated in vascular events. Although several studies were done it is very difficult to assess the prognosis of stroke. Several indicators like site of infarction, size of infarct, vessel involved, Glasgow coma scale (GCS) and oedema around the infarct to assess the severity and prognosis of ischemic stroke and in haemorrhagic stroke it includes Glasgow coma scale, and volume of haemorrhage based on CT scan and location of haemorrhage.

For a Long time, serum ferritin was measured only to know the stored Iron status. Now it has been recommended that it influences the prognosis of ischemic stroke<sup>1</sup> and also acts as a risk factor for ischemic episodes by enhancing atherogenesis.<sup>2,3</sup> In our study serum ferritin is assessed to evaluate the neurological deterioration and prognosis in

patients of acute stroke. Therefore, measuring of serum ferritin is useful in identifying high risk patients.

## 2. Objectives

1. To study the effect of level of serum ferritin with early neurological deterioration and the outcome in patients of acute stroke.
2. Association of serum ferritin in ischemic and haemorrhagic stroke.

### 2.1. Study setting

This study was be done at Sri Manakula Vinayagar Medical College and Hospital (SMVMCH), Puducherry, under the department of General Medicine during the year 2018-20 after getting institution ethics committee approval. This is a hospital based analytical cross-sectional study. Sample size of this study was 50.

### 2.2. Inclusion criteria

1. All cases of acute cerebrovascular accident patients from 18 to 80 years admitted as inpatients in wards of general medicine department.
2. Diagnosis of CVA confirmed by CT or MRI scan of brain.
3. Patients should present within 48hrs of onset of symptoms.

### 2.3. Exclusion criteria

1. Patients with anaemia.
2. Patients with history of malignancy.
3. Patients with liver disease or renal disease.
4. Patients with recent myocardial infarction within < 4 weeks.
5. Patients with history of previous stroke or intracranial haemorrhage.
6. Patients with k/c/o of rheumatoid arthritis or SLE.
7. Patients with h/o of fever.
8. Patients presenting after 48 hrs of onset of symptoms.

### 2.4. Study procedure

50 patients with acute stroke were selected based on inclusion and exclusion criteria. Appropriate questionnaire was used to collect data of patients. Diagnosis of stroke was confirmed by CT or MRI scan of brain plain and examination was done by Canadian stroke scale at the time of admission. About 5ml of venous blood Sample from cubital vein was collected for measuring serum ferritin levels, it was performed within 48hrs of onset of symptoms by using CLIA method. Neurological assessment was repeated on the day of discharge to assess the clinical improvement and prognosis of the stroke patients.

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The data obtained from the proforma was entered into Microsoft excel and analysed using statistical package for social sciences version 16. A p value of less than 0.05 was considered statistically significant.

Section A- Patient Alert Or Drowsy

Date			
Time			
M E N T A L F U N C T I O N	LEVEL CONSCIOUSNESS: Alert(0)		
	Drowsy(1.5)		
	ORIENTATION: Oriented(1)		
	Disoriented or Non Applicable(0)		
S P E E C H	SPEECH: Normal(1)		
	Expressive Deficit(1.5)		
	Receptive Deficit(0)		
<b>MOTOR FUNCTIONS:</b>			
<b>WEAKNESS:</b>			
S E C T I O N  A <sub>1</sub>	F A C E:	None(.5)	
		Present(0)	
	A R M: P R O X I M A L	None(1.5)	
		Mild(1)	
		Significant(.5)	
		Total(0)	
	A R M: D I S T A L	None(1.5)	
		Mild(1)	
		Significant(.5)	
		Total(0)	
	L E G:	None(1.5)	
		Mild(1)	
Significant(.5)			
Total(0)			
S E C T I O N  A <sub>2</sub>	M O T O R R E S P O N S E:	FACE: Symmetrical(.5)	
		Asymmetrical(0)	
	A R M S:	Equal(1.5)	
		Unequal(0)	
	L E G S:	Equal(1.5)	
		Unequal(0)	

Chart 1: Canadian Stroke Scale

**3. Results**

Table 1 shows the distribution of the demographic characteristics of the patients with stroke. Majority of the patients were belonging to the age group of 51-60 years (36%) and were males (70%).

Table 2 shows the distribution of the behavioral risk factor profile of the patients. More than one-third of the patients were smokers (38%) and consuming alcohol (36%).

Table 3 shows the distribution of the comorbidities among the patients. Nearly half of the patients had diabetes mellitus, 52% had hypertension and 8% had cardiovascular disease.

Table 4 shows the distribution of serum ferritin levels among the patients with stroke. About 18% of the patients had high serum ferritin levels. The median serum ferritin value is 101.60 mg/dl.

Table 5 shows the lipid profile and the distribution of biochemical parameters among the stroke patients. About 18%, 38%, 10%, 14% and 30% patients had high cholesterol, triglycerides, LDL cholesterol, HDL cholesterol and VLDL cholesterol, respectively.

Table 6 shows the distribution of stroke profile of the patients. Majority (90%) of the patients had ischaemic type of stroke while only 6% showed haemorrhagic transformation. Anterior circulation vessels were affected

in most (74%) of the patients and more than half (52%) presented hemiplegia on the right side. Carotid stenosis was present in 6% of the patients while it was not done in 64% of patients.

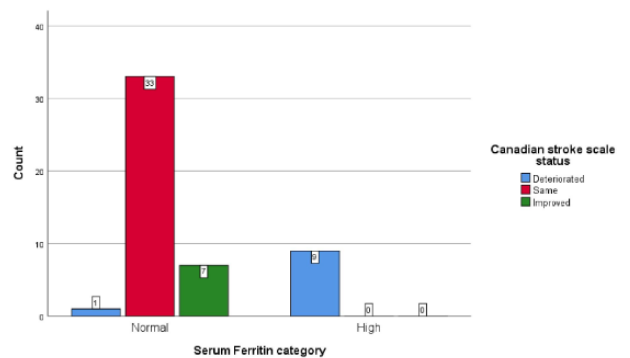
Table 7 shows the Canadian stroke scale interpretation on the day of discharge among the stroke patients. The stroke scale status deteriorated in 20% of the patients while remained the same in majority (66%) of the stroke patients.

Table 8 shows the association and distribution of the serum ferritin levels with Canadian stroke scale status. High serum ferritin levels have been significantly associated with deterioration in Canadian stroke scale status (p<0.001) when compared to those with normal serum ferritin levels.

Figure 1 shows the association and distribution of the serum ferritin levels with Canadian stroke scale status. High serum ferritin levels have been significantly associated with deterioration in Canadian stroke scale status (p<0.001) when compared to those with normal serum ferritin levels.

Table 9 shows the association and distribution of the serum ferritin values with Canadian stroke scale status. Those with deteriorated Canadian stroke scale status had significantly high serum ferritin levels (p<0.001) when compared to other status groups. Canadian stroke scale status groups.

Figure 2 shows the association and distribution of the serum ferritin values with Canadian stroke scale status. Those with deteriorated Canadian stroke scale status had significantly high serum ferritin levels (p<0.001) when compared to other status groups. Canadian stroke scale status groups.



**Fig. 1:** Distribution of the Canadian stroke scale status among the serum ferritin level (n=50)

**4. Discussion**

This study was done to find the association of serum ferritin as a prognostic factor in acute cerebrovascular accident. The sample size of this study is 50, who are admitted under general medicine and neurology department in Sri Manakula Vinayagar medical college and hospital. Serum ferritin and neurological assessment by Canadian stroke

**Table 1:** Baseline demographic characteristics of the patients (n=50)

Variable	Categories	Number	Percentage
Age category	≤50 years	7	14
	51-60 years	18	36
	61-70 years	15	30
	>70 years	10	20
Gender of the patient	Male	35	70
	Female	15	30

**Table 2:** Behavioral risk factor profile of the patients (n=50)

Variable	Categories	Number	Percentage
Smoking status	Yes	19	38%
	No	31	62%
Alcohol consumption	Yes	18	36%
	No	32	64%

**Table 3:** Morbidity profile of the patients (n=50)

Variable	Categories	Number	Percentage
Diabetes Mellitus	Present	23	46%
	Absent	27	54%
Hypertension	Present	26	52%
	Absent	24	48%
Heart disease	Present	8	16%
	Absent	42	84%

**Table 4:** Serum ferritin profile of the patients (n=50)

Levels, n(%)	Serum ferritin	
	Normal	41(82)
High	9(18)	
Mean (SD)	161.07(160.73)	
Median (IQR)	101.60(42.43-233.70)	

**Table 5:** Lipid profile of the patients (n=50)

Variable	Categories	Number	Percentage
Total cholesterol	Normal	41	82%
	High	9	18%
Total triglyceride	Normal	31	62%
	High	19	38%
	Low	13	26%
LDL cholesterol	Normal	32	64%
	High	5	10%
	Low	28	56%
HDL cholesterol	Normal	15	30%
	High	7	14%
VLDL cholesterol	Low	5	10%
	Normal	30	60%
	High	15	30%

**Table 6:** Distribution of stroke profile of the patients (n=50)

Variable	Categories	Number	Percentage
<b>Type of stroke</b>	Ischaemic	45	90%
	Haemorrhagic	5	10%
<b>Haemorrhagic transformation</b>	Present	3	6%
	Absent	47	94%
<b>Vessels affected</b>	Anterior circulation	37	74%
	Posterior circulation	3	6%
	Lacunar	10	20%
<b>Side of Hemiplegia</b>	Right	26	52%
	Left	21	42%
	No weakness	3	6%
<b>Carotid stenosis</b>	Normal	15	30%
	Present	3	6%
	Not done	32	64%

**Table 7:** Canadian stroke scale interpretation on the day of discharge (n=50)

Variable	Categories	Number	Percentage
Canadian stroke scale status	Deteriorated	10	20%
	Same	33	66%
	Improved	7	14%

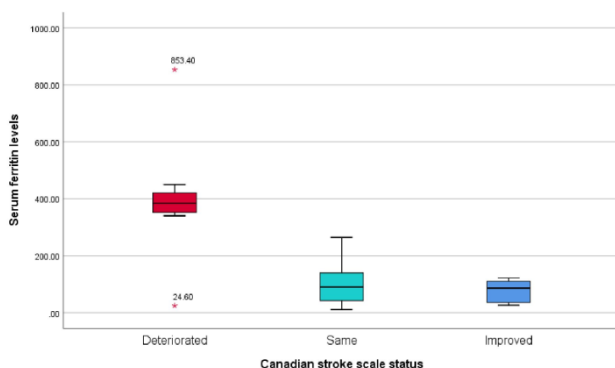
**Table 8:** Association of the serum ferritin levels with Canadian stroke scale status (n=50)

Serum Ferritin category	Normal High	Canadian stroke scale status			Chi-square (p value)
		Deteriorated	Same	Improved	
		1 (2.4)	33(80.5)	7(17.1)	43.902 (<0.001)
		9 (100.0)	0	0	

**Table 9:** Association of the Canadian stroke scale status with serum ferritin values (n=50)

Canadian stroke scale status	Deteriorated Same Improved	Serum ferritin levels		p value*
		Mean (SD)	Median (IQR)	
		398(199.29)	383.65(352.4-420.2)	<0.001
		107(76.77)	90.00(42.43-139.80)	
		75(41.56)	86.40(34.40-117.10)	

\*p value by Kruskal-Wallis test



**Fig. 2:** Distribution of the serum ferritin value among the Canadian stroke scale group (n=50)

scale was done in all patients. The sample size of this study was nearly equal to the study conducted by SK Mandal, Ashlian Kusvuran Ozkan et al.<sup>4</sup>

In this study it is observed that majority of the subjects are males 35 (70%), and females are 15(30%), and 36% were in the age group of 51-60 years, 30% between 61-70 years of age group and 20% is more than >70 years, and 14% are age less than 50 years. So, in this study majority of the stroke patients are in the age group of 51-60 years.

Similar study was conducted by Dr.Siddharth Kapoor et al, it was a prospective cohort study in that study 23 stroke patients were selected. In which males were 60.86% and females were 39.14%, majority of the subjects were in the age group of 51-60 years. Another study which was conducted by Hemant Mahur et al.,<sup>5</sup> in that study males were 59.67% and females were 30.62% which is similar to our study. But in our study age and gender is not significantly associated with serum ferritin levels and

Canadian stroke scale. In our study 38% of the subjects are smokers and 64% are alcoholics. Only alcohol consumption was significantly associated ( $p=0.034$ ) with higher serum ferritin levels and with deterioration of Canadian stroke scale status. A study done by Elizabeth Mostofsky et al.,<sup>6</sup> showed that heavy alcohol consumption increases the risk of stroke. In our study, out of 50 subjects 46% had diabetes mellitus and 52% had hypertension. Among them three diabetic patients and five hypertensive patients had high ferritin levels. A study of clinical profile of stroke was done by Daad H Akbar et al.,<sup>7</sup> to determine the pattern and risk factors of stroke in Saudis and non-saudis population, it showed hypertension is the more common risk factor for both ischaemic and hemorrhagic stroke. In our study among 50 subjects 26 patients had hypertension but there is no positive correlation between serum ferritin and Canadian stroke scale status with diabetes and hypertension. The mean duration of both diabetes and hypertension is 5 years.

In this study Out of 50 patients, the 8 patients (16%) are diagnosed to have heart disease. About 14% of the patients had coronary artery diseases and 2% have valvular heart disease. There was no significant correlation of heart disease with serum ferritin and Canadian stroke scale status. None of the lipid profile parameter were significantly associated with serum ferritin and Canadian stroke status which is similar to the study done by Joshua Z. Willey et al.<sup>8</sup> In our study ischemic stroke was seen in 45 (90%) of the patients and 5 (10%) were seen in hemorrhagic stroke. The serum ferritin levels were found to be normal in 41(82%) subjects and were high in 9(18%) subjects. The mean ferritin level was 161.07ng/mL. Those patients with hemorrhagic stroke 60.0% had significantly higher ferritin levels and higher deterioration in Canadian stroke scale status ( $p=0.041$ ) when compared with ischemic stroke. A study done by Yee Sien Nget al.,<sup>9</sup> the study showed. That the incidence of anterior circulation stroke is twice that of posterior circulation and small vessel stroke which is similar to our study. None of the stroke profile parameter like types of stroke and vessel affected were significantly associated with serum ferritin level and Canadian stroke scale status.<sup>10</sup> The Canadian stroke scale interpreted at the time of discharge to assess the prognosis of the patient from initial status shows deterioration in 20% of the patients and 66% of the patients remained in the same status and 14% of the patients were improved.

#### 4.1. Association of serum ferritin levels with Canadian stroke scale status

Among 50 patient serum ferritin levels are normal in 82% and high in 18%. The mean serum ferritin level is 161.07. The Canadian stroke scale interpretation at the time of discharge showed 20% of the patients are deteriorated, 66% are under same status and 14% of the patients are improved. Those patients with hemorrhagic stroke had significantly

higher serum ferritin level (60.0%)  $p=0.010$  when compared with those of ischemic stroke (13.3%). Hemorrhagic stroke patients (60.0%) had higher deterioration in Canadian stroke status when compared with ischemic stroke (15.6%). Association of serum ferritin levels with Canadian stroke scale shows that high serum ferritin levels have been significantly associated with deterioration in Canadian stroke status ( $p<0.001$ ) when compared to those with normal serum ferritin levels. The mean serum ferritin levels are higher in deteriorated patients 199.29% when compared to other Canadian stroke scale status groups.

## 5. Conclusion

1. This study is a cross sectional study, of association of serum ferritin as a prognostic marker in acute cerebrovascular accident.
2. This study showed that among 50 subjects, only 9(20%) patients have high serum ferritin levels. The serum ferritin levels are high in hemorrhagic stroke (60.0%) when compared to ischemic stroke (13.3%). In Canadian stroke scale status higher deterioration was seen in hemorrhagic (60.0%) stroke when compared with ischemic stroke (15.6%). In this study we had only minimal number of patients have hemorrhagic stroke (10%) hence association cannot be accurate.
3. This study showed that the significant rise in serum ferritin levels in hemorrhagic stroke patients it correlates with decrease score in Canadian stroke scale (CSS) which indicates the severity. The mean serum ferritin levels are higher in deteriorated patients 199.29% when compared to other Canadian stroke scale status groups.
4. Elevated serum ferritin levels have been significantly associated with deterioration in Canadian stroke scale status ( $p<0.001$ ) when compared to those with normal serum ferritin levels. It reveals the poor outcome in patients with high serum ferritin levels.
5. This study shows male predominant, more patients with in the age group of 51-60 years.
6. Only alcohol consumption was significantly associated ( $p=0.034$ ) with higher serum ferritin levels and with deterioration of Canadian stroke scale status.

## 6. Limitations

1. Less sample size.
2. Hemorrhagic stroke patients are (10%), hence association cannot be significantly correlated.

## 7. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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None.

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