ORIGINAL RESEARCH

To determine serum ferritin as prognostic marker in intracranial hemorrhage: A prospective study

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ABSTRACT

Background: Monitoring of ferritin levels plays a crucial role in the management of various disorders and the evaluation of therapy efficacy. In addition, serum ferritin's predictive value extends beyond disease progression.

Aim: The present study aim is to determine the serum ferritin levels in acute hemorrhagic stroke patients, between different prognostic groups, and also to correlate the levels with severity of acute hemorrhagic stroke.

Materials & methods: This study was conducted in VIMSAR, Burla from December 2018 to November 2020. This was a hospital based observational study. A group of 60 subjects participated in this study. Clinical evaluation was carried out noting vital parameters, clinical signs of focal neurological deficit and signs of increased intracranial tension. Other systems were also examined to find significant comorbidities. All patients were treated according to the established guidelines at the time of study.

Results: In the good prognosis group, fifty percent of patients had their serum ferritin values in the range of 200 – 300 ng/ml. Five patients had their serum ferritin value more than 400 ng / ml. The mean serum ferritin value was 290.7 ng/ml (SD 98.06). This difference is statistically significant ($P < 0.05$). On comparison, serum ferritin values are found to be statistically high in mortality group followed by bad prognostic group. 7 patients (77.7%) in the good prognostic group had their ferritin value less than 200 ng/ml. The mean serum ferritin value was 144. 7 ng/ml (SD 90.95). This is statistically significant with $P < 0.05$. Among dead, the majority (61.9%) have serum ferritin in the range of 300-400 ng/ml, followed by 23.8% have value more than 400 ng/ml. The mean serum ferritin value was 355.4 ng/ml (SD 82.8). This difference is statistically significant ($P< 0.05$).

Conclusions: we conclude that the baseline serum ferritin can be used as an independent prognostic marker. The increased body iron stores as measured by ferritin is associated with clinical deterioration.

Keywords: Cerebrovascular diseases; Stroke; Intracranial haemorrhage; Aneurysms; Hypertension; Diabetes.

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Introduction

Cerebrovascular disease is one of the most devastating neurological diseases. The term stroke is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause[1]. The stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. Cerebrovascular diseases include the infarction through occlusion of major arteries, small arteries or venous sinuses and hemorrhage, most often through rupture of small arteries, arterioles, aneurysms or capillaries [2,3]. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. The consequence of stroke is devastating. Apart from the functions specific to the lost brain tissue, other essential mental faculties such as humor, mood, initiative, and speed of thought are severely affected. Sadly, these attributes are ignored in the treatment of stroke patients.

Strokes are common with an annual incidence of 42-100/10000. It is the second most common cause of death in Europe after heart failure. It is the third most common cause of death after heart failure and cancer in united states. Overall, it is the second most common cause of death worldwide and a major cause of disability[4]. The cumulative incidence of stroke in India ranges from 105 to 152 per 1 lakh population per year and the crude prevalence of stroke ranges from 44.29 to 559 per 1 lakh population in different parts of the country during the last decade (2010-20)[5].

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Serum ferritin is a protein that stores iron in the body. It plays a crucial role in iron homeostasis and is often used as a marker to assess iron status [6]. However, in recent years, there has been growing interest in understanding the potential role of serum ferritin as a prognostic marker in various medical conditions [7]. Studies have shown the measurement of serum ferritin levels has the potential to provide valuable information regarding the advancement or intensity of a given disease [8-10]. Elevated serum ferritin levels have been observed in several iron load illnesses, such as thalassemia, hemolytic anaemias, inflammatory disorders, malignancies, and neurological disorders [8]. Across the world studies implies that monitoring of ferritin levels plays a crucial role in the management of various disorders and the evaluation of therapy efficacy. In addition, serum ferritin's predictive value extends beyond disease progression. It has also been investigated as a predictor of complications, such as cardiovascular events or organ dysfunction. Identifying patients at higher risk of adverse outcomes based on their ferritin levels can facilitate early intervention and personalized care. Hence, the present study aim is to determine the serum ferritin levels in acute hemorrhagic stroke patients, between different prognostic groups, and also to correlate the levels with severity of acute hemorrhagic stroke.

Materials & Methods:

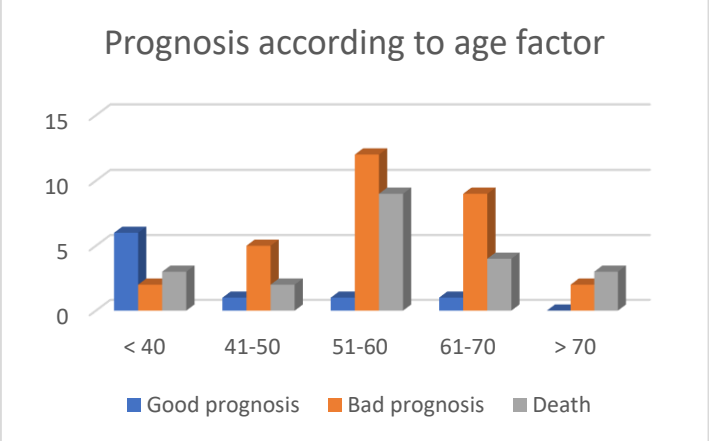
This study was conducted in VIMSAR, Burla from December 2018 to November 2020. This was a hospital based observational study. A group of 60 subjects participated in this study. Inclusion criteria for study patients: Acute cerebral hemorrhage diagnosed clinically and by computed tomography or magnetic resonance imaging of brain. Exclusion criteria for study patients: patients having ischemic stroke, anemia, severe alcohol consumption, chronic liver disease, chronic kidney disease, hematological cancer, and secondary intracerebral hemorrhage were excluded. A standard proforma designed for the study was used. On admission, a complete history was obtained from every patient including symptoms of headache, vomiting, loss of consciousness, seizures and focal neurological deficit. History of hypertension, diabetes mellitus, drug history including use of anticoagulation were noted. Clinical evaluation was carried out noting vital parameters, clinical signs of focal neurological deficit and signs of increased intracranial tension. Other systems were also examined to find significant comorbidities. All patients were treated according to the established guidelines at the time of study. All the patients were subjected to non-enhanced computed tomography scan of the brain. Cases of primary intracerebral hemorrhage were selected. The location of the hematoma, presence of midline shift and intraventricular extension of bleed were assessed. After getting informed consent from all the participants, 2ml of venous blood was collected by sterile venepuncture within 72 hours of symptom onset. Serum ferritin levels were estimated by ELISA method. Simultaneously renal function, liver function and complete blood count and peripheral smear study were carried out. Evaluation of prognosis was done. All the study patients were assessed using the modified Rankin scale on the 5th day of admission and then again on the 15th day of follow up. The score of 0-2 was considered good prognosis. The score of 3-5 was considered bad prognosis and the score 6 was given to the event of death. Estimation of serum ferritin levels using quantitative classic sandwich ELISA assay using Accubind serum ferritin kit of Monobind INC. U.S.A. It is immune-enzymometric sequential assay type 4.

Statistical Analysis:

The variables were analysed using SPSS software version 15. Students t-test and chi square tests were employed to find out significance of difference between means in study patients. Variables are analysed using one way ANOVA between different prognostic groups.

Results:

Figure 1: Age wise distribution among different group



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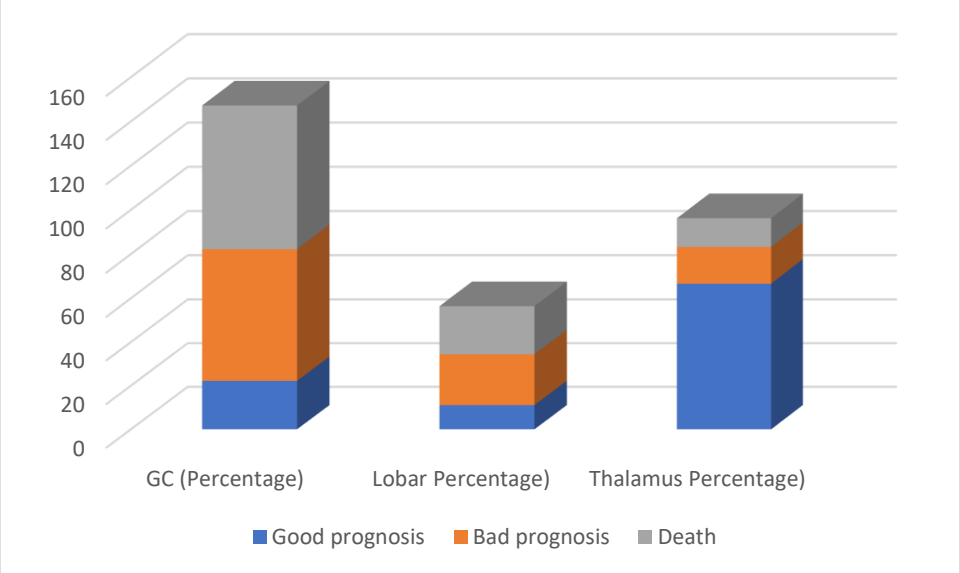
Majority of the patients belong to the age between 51 to 70 years. The minimum age was 32 years and maximum age was 80 years. Out of this, male constituted 45 in number and 15 in number. Most patients in the good prognostic group fall below 40 years of age. Many patients in the bad prognostic group lie between 51-70 years of age group. The overall mortality is 35% and most death is occurring in the age group of 51-70.

Table 1. Risk factors among the study population

Risk factors	Frequency	Percentage
Hypertension	55	92
Diabetes	18	30
Smoking	14	24
Alcohol	24	40

In the group of patients among good prognosis, 5 belong to hypertensive (HTN) and 1 was of diabetes. In the group of patients among bad prognosis, 29 belong to HTN and 7 were of diabetes. In the group of patients among dead, 21 belong to HTN and 8 were of diabetes.

Figure 2: Location of hematoma in different groups of the study



The most common location of hematoma in the study population is GC (GC) region and is most consistent with the site of hypertensive haemorrhage (62%). The lobar is least affected in the study (14 %). Among good prognostic group, most have hematoma in thalamic area followed by GC and least in lobar area. Among bad prognostic group, majority (60%) have hematoma in GC region followed by Lobar and Thalamic region. The majority among dead had haemorrhage in GC region (65%) followed by Lobar (22%) and least in Thalamus (13%).

Table 2: Symptoms among all patients

Symptoms	Frequency	Percentage
Focal neurological deficit (FND)	60	100
Headache	28	46
Vomiting	16	26
LOC	24	40
Seizure	10	16

100% of patients had focal neurological deficit, 46% had headache, 26% had vomiting. Loss of consciousness was present in 40% of patients while only 16% had seizure episodes.

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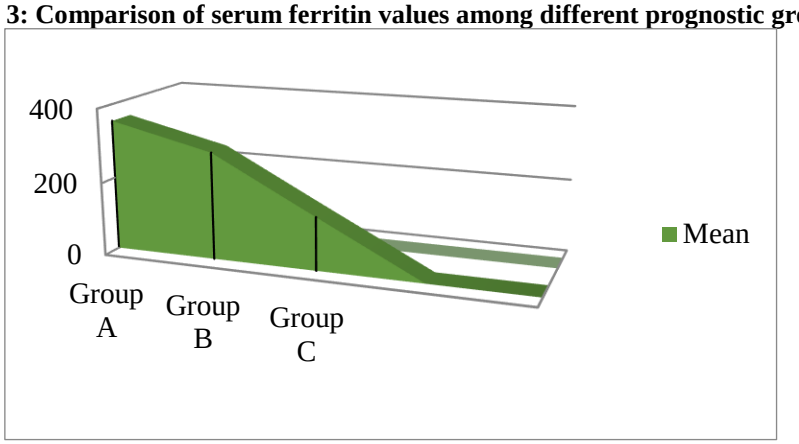
Figure 3: Comparison of serum ferritin values among different prognostic groups.



In the good prognosis group, fifty percentage of patients had their serum ferritin values in the range of 200 – 300 ng/ml. Five patients had their serum ferritin value more than 400 ng / ml. The mean serum ferritin value was 290.7 ng/ml (SD 98.06). This difference is statistically significant ($P < 0.05$). On comparison, serum ferritin values are found to be statistically high in mortality group followed by bad prognostic group. 7 patients (77.7%) in the good prognostic group had their ferritin value less than 200 ng/ml. The mean serum ferritin value was 144. 7 ng/ml (SD 90.95). This is statistically significant with $P < 0.05$. Among dead, the majority (61.9%) have serum ferritin in the range of 300-400 ng/ml, followed by 23.8% have value more than 400 ng/ml. The mean serum ferritin value was 355.4 ng/ml (SD 82.8). This difference is statistically significant ($P< 0.05$).

Discussion:

This study was conducted on 60 patients with acute intracerebral hemorrhage to find out the serum ferritin levels and correlation between different prognostic groups. In the previous studies by William Whitely *et al* [(116)], the other variables that are associated with poor outcome include, body temperature, blood glucose, C- reactive protein (C-RP), WBC, serum cortisol, elevated plasma and CSF levels of glutamate, glycine and IL-6. It is likely that the inflammatory response is triggered by stroke process and mediated by IL-1 (fever) and IL-6 / TNF with rise in acute phase reactants such as C-RP etc. that may enhance neurotoxicity. However, the initial rise in serum ferritin levels at the onset of stroke is not associated with inflammatory response and correlates with the body iron stores. In the study by Natalia Perez *et al*, it has been proved that the serum ferritin levels are not correlated with other markers of inflammatory response [11]. It is again confirmed by Armengolu*et al*[12].

Yang *et al* [13] has also proved an association between increased body iron stores as measured by serum ferritin and clinical deterioration of acute cerebral infarction. The beneficial effect of iron chelation by deferoxamine has been proved in experimental animals by independent investigator; Masanobu et.al.[14] in rats and Yuxianggu [15] in piglets. No adverse effects were found in humans with desferoxamine infusion by Magdyselim [16]. So, if the role of Iron in Intracranial haemorrhage (ICH) is proved by many studies with large sample size, the role of iron chelation can be studied in future. In this current study of 60 patients with ICH admitted in our hospital, the incidence of ICH is high among the age group of 51 – 70 years. Males are more commonly affected 3 times higher than females (3:1). Hypertension is the most associated risk factor (92%) in this study population. It is similar to the other study series and is the most common cause of ICH worldwide as reported by Caplan and Kase [17]. Diabetes mellitus is present in 30 % of the study population. The most common location of hypertensive ICH is lateral GC region. In a clinicopathological series by Cole and Yates [18], it has been found that the microaneurysms caused by hypertension were commonly located in this region. In our study, the most common location of ICH is GC region followed by lobar and thalamus. Older patients are having little higher incidence of lobar haemorrhage located in tempero-parietal region. The cerebral amyloid angiopathy as a cause of lobar haemorrhage in older age group cannot be ruled out in the absence of follow up and histo-pathalogical correlation. Headache is the second most common symptom after focal neurological deficit. It is present in 46% of the study population. The overall mortality is 35 % in this study population. This is also higher than the reported mortality rate of 10 – 20 % among developed countries. In part it can be explained by lack of long-term care facilities in most part of India and associated complications of immobilization. The high mortality occurs in age group of 51 – 70 years in this study population (66 %). 13 out of 36 patients in this age group died due to ICH. The serum ferritin levels are significantly elevated among the bad prognostic group with Modified Rankin Score of more than 2. The mean serum ferritin value in good prognosis is 144.7 ng/ml (SD 90.95). The mean ferritin values are 290.7ng/ml (SD 84.04) and 355.4 ng /ml (SD 82.8) in patients with MRS 3 to 5 and 6 respectively. The difference is statistically significant

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($p < 0.05$). Hence the serum ferritin level at the baseline can be used as a prognostic marker in ICH. This is similar to the results obtained by Natalie et.al in his study. The mean ferritin value in that study was 270.6 ng/ml in bad prognostic group[43]. The difference is statistically significant with $P< 0.05$. The results obtained by this study are close in numbers and similar in nature to the studies conducted by Natalie *et al* [19], Armengou*et al* [11], Davlos*et al* [20] and Whitely *et al* [21].

Conclusion:

In our study of 60 patients with acute intracerebralhaemorrhage, we conclude that the baseline serum ferritin can be used as an independent prognostic marker. The increased body iron stores as measured by ferritin is associated with clinical deterioration. Hypertension is the most common risk factor associated with ICH. The most common site of bleeding is GC region. The absence of diabetes and younger age are factors associated with good prognosis. Headache is the 2nd most common presenting symptom followed by focal neurological deficit. Males are more commonly affected than females. In the good prognosis group, most common site of involvement is Thalamus. Among patients in the good prognosis group, most are under 40 years of age. However, more research about this topic may highlight further knowledge in future.

Conflict of interest: None.

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