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A Prospective Study to Determine Serum Ferritin as a Biomarker for Prognosis of Patients with Acute Hemorrhagic Stroke

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Abstract
Aims and Objective :*Intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality in India. As previous studies show association between high serum ferritin and poor outcome in ischemic stroke ,we decided to determine admission time serum ferritin level as a prognostic biomarker of functional outcome of patients with ICH .*
Methods :*100 patients with ICH were selected within 48 hours of admission to department of medicine and neurology , SCBMCH between 2017 to 2019 . ICH is confirmed by NCCT of brain and at admission serum ferritin was measured by CLIA method. Functional outcome of patients was determined by Canadian Stroke Scale at day 0th and day 7th . Results were analyzed by appropriate statistical methods.*
Results : *Mean serum ferritin level of group of patients who improved was 79.20 ng/ml and those who deteriorated or died was 158.80 ng / ml .There is statistically significant difference between means of these two groups .*
Conclusion : *Mean serum ferritin level may be a useful prognostic biomarker of acute hemorrhagic stroke .*
Key Word: *CLIA, Canadian stroke scale, functional outcomes, ferritin.*

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I. Introduction

WHO has defined stroke as "rapidly developed clinical sings of focal disturbances of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than vascular origin".[1] Stroke include numbers of syndromes with differing etiology, epidemiology, prognosis and treatment.

Stroke is the second leading cause of death worldwide with 6.2 millions dying from stroke in 2015.[2] In developed countries, stroke is the first leading cause of disability, second leading cause of dementia and third leading cause of death. Stroke is also a predisposing factor for epilepsy, falls and depression in developed contries[5] and a leading cause of functional impairment. But low and middle income countries account for 85.5% of total stroke death worldwide [6] and the numbers of DALYs in these countries was approximately seven times than that of high income countries[7].

The estimated adjusted prevalence rate of stroke in India ranges from 84 – 262/10000 in rural area and 334 – 145 / 10000 based on recent population based study.[3]

Global Stroke Estimates :

- 16 million new acute strokes every year [7]
- 11.8% of all deaths 2013.
- 6.5 million death from stroke[8]

Indian Stroke Statistic :

Prevalence :147 – 922 / 100000 [9]
Mean age :66 – 67 years [4,10]
Young Stroke (< 40 yr age) :3.8% [10]
Men higher incidence than women; age standardized incidence rate is 162 / 10000 person year for men vs 141 / 10000 person years for women [4]
Ischemic 80.2% hemorrhagic 17.7% [4]

Risk factors : Hypertension (54%), hypercholesterolemia (15%), tobacco smoking (12%) [7].

Intracerebral Hemorrhage :

Intracerebral hemorrhage (ICH) causes 10 to 15% of all brain strokes. The amount of mortality and morbidity caused by ICH within 30 days is average 44%. Incidence rates are high in Asian. Data from the Asian Stroke Advisory Panel has revealed an incidence of ICH ranging from 17 to 33% of all strokes, twice as high as in Western countries.

Intracranial hemorrhage and serum ferritin :

In intracranial hemorrhage after blood releases from blood vessels, enters into brain parenchyma. In the parenchyma, the blood releases it's serum and during this process ferritin is also released. Therefore ferritin may be related to blood or iron volume which exists in brain tissue and it may indirectly relates to the oxidative injury that it causes.

As serum ferritin is directly proportional to tissue iron store and in brain tissue iron, in the form of ferritin is localized in astrocyte and microglia. In Cerebrovascular diseases oxygen superoxide radicals increases the amount of iron in the cytosol from ferritin. Iron can initiate and propagate lipid per- oxidation leading to altered membrane fluidity, inactivation of membrane bound enzyme complexes eventually forming edema , membrane disruption and cell death. The amount of lipid per-oxidation is considered to depend on the concentration of iron store .Clinical studies have shown an association between high ferritin level in blood and poor outcome in stroke. Few studies are done to determine prognosis of acute hemorrhagic stroke patients using serum ferritin as a biomarker. The outcome of patients is defined as survived (improved) or deteriorated or deceased. As there is very few studies are done in India to determine role of serum ferritin as prognostic biomarker in intracranial hemorrhage, we have decided to determine admission time serum ferritin level as a prognostic biomarker of functional outcome of a cohort of patients of intracranial hemorrhage.

II. Aims And Objectives

1) To estimate serum ferritin in patients with acute hemorrhagic stroke.
2) To determine association of serum ferritin level at the time of admission with functional outcome of patients with acute hemorrhagic stroke at day 7.
3) To establish the role of serum ferritin as a bio marker of severity and prognosis of acute hemorrhagic stroke.

III. Materials And Methods

Selection of cases :

100 patients with acute hemorrhagic stroke within 48 hours of onset of symptoms, who were admitted to department of medicine and department of neurology at SCBMCH during study period of December 2017 to December 2019 were selected for study. All patients were evaluated with detailed history, examination and relevant laboratory tests.

Study Design :

Prospective cohort study.

Inclusion Criteria

(1) Age greater than 18 years old
(2) Both male and female
(3) Presented within 48 hours of onset of symptoms
(4)Diagnosis of stroke will be confirmed by non-contrast CT scan of brain.

Exclusion Criteria

Patients with
1) Ischemic strokes
2) Intra-ventricular and subarachnoid hemorrhages
3) Body temperature greater than 37.5 C
4) Infection
5) Malignancy
6) Liver diseases
7) Anemia
8) Autoimmune disorders

Investigations :

At the time of admission routine laboratory tests (complete blood counts, serum electrolyte, blood sugar, liver function tests, lipid profile, urine analysis), chest radiographs, 12 lead ECG, 2D echo of heart were done in all patients.

NCCT scan was done in all patients to determine ischemic or hemorrhagic stroke. USG abdomen and pelvis, MRI angiogram were done in patients as and when required.

Serum ferritin level was measured by CLIA (Chemiluminescence immunoassay) method at the department of biochemistry of these patients. Chemiluminescence Immunoassay (CLIA) detection using Microplate-luminometers provides a sensitive, high through output, and economical alternative to conventional colorimetric methodologies. CLIA has been shown to bemore sensitive than the conventional colorimetric method(s) .Among various enzyme assays that employ light-emitting reactions, one of the most successful assays is the enhanced chemiluminescence immunoassay involving a horseradish peroxidase (HRP) labeled antibody or antigen and a mixture of chemiluminescent substrate, hydrogen peroxide, and enhancers. The CLIA Kits are designed to detect glow-based chemiluminescence reactions. The kits provide a broader dynamic assay range, superior low-end sensitivity, and a faster protocol than the conventional colorimetric methods.. There is minimal cross-reactivity with human serum albumin, alpha-fetoprotein, human hemoglobin, human transferrin, and ferric chloride. The Elecsys Ferritin Kit utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the intact ferritin molecule. Mouse monoclonal anti-ferritin antibody is used for solid phase (micro-titer wells) immobilization and a goat anti-ferritin antibody is in the antibody-enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the ferritin molecules being sandwiched between the solid phase and enzyme-linked antibodies. A solution of chemiluminescent substrate is then added and read relative light units (RLU) in a luminometer. The intensity of the emitting light is proportional to the amount of enzyme present and is directly related to the amount of ferritin in the sample.

Sample material : Serum collected using standard sampling tubes.
Sample volume – 10 microliter
Normal range – 30 - 400 ng / ml

Management:

Management during the hospital stay included control of hypertension with appropriate antihypertensives to maintain a systolic blood pressure of< 140 mm of Hg , treatment of raised intracranial pressure with mannitol, maintenance of airway, oropharyngeal suction, and Ryle's tube aspiration, and general supportive measures to prevent bed sore, contractures. Intercurrent infections and as any other complications were treated as per requirements.

Functional Outcome of Patients:

Canadian stroke scale (CSS) is a simple validated score to assess stroke severity .Though Glasgow Coma Scale was developed as a standardized method for the periodic evaluation of head injury patients. The emphasis of this scale in neurological deficits is not frequently found in acute stroke patients (i.e. failure of eye opening, decerebration, decortication). Important modalities such as dysphasia and gradation of motor deficits are not included. Clearly this type of scale does not apply specifically to acute stroke. The Canadian stroke scale tests 10 simple clinical modalities. Under the section on mentation, one evaluates in all patients, first the level of consciousness, then orientation and speech. The next 7 items can be regrouped in two sections based on the presence or absence of a comprehension defect. If a patient has no comprehension defect, he or she is scored using section A1 which tests motor function in the face, arm proximal and distal and in the legs. However, if a comprehension defect is present, section A2 is used to evaluate motor response in the face, arms and legs. In general, a clinician takes between 5 and 10 minutes to assess completely each patient using the scale described. The previous studies showed good to excellent inter-rater agreement (kappa or weighted kappa score 0.76-1.00)[23].

Severity of stroke was determined by Canadian stroke scale within 48 hours of onset of symptoms. Functional outcome of patients was measured by Canadian stroke scale on day [23].

Statistical Analysis :

Pair wise comparison between various variable was done for different parameters. The Range, Mean value, Standard Deviation (S.D.), Standard error of Mean, t-value and p-values were calculated as per the applicability by using appropriate formulas. Statistical Package of Social Sciences (SPSS) v. 22 was used for the purpose of data entry and data analysis. Chi-square test was used to find out associations (relations) between categorical variables, ANOVA test was used to find out associations between multiple categorical variables. Pearson's correlation coefficient was used for numerical variables. P-value less than 0.05 was regarded as statistically significant.

Date **Time**						
Mentation		Level of Consciousness	Alert	3		
			Drowsy	1.5		
		Orientation	Oriented	1		
			Disoriented or Non-applicable	0		
		Speech	Normal	1		
			Expressive Aphasia	0.5		
			Receptive Aphasia	0		
Section A1	No comprehensive Deficit	**Motor Functions :**	**Weakness :**			
		Face	None	0.5		
			Present	0		
		Arm : Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Arm : Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg : Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg : Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
Section A2	Comprehensive Deficit	Face	Symmetrical	0.5		
			Asymmetrical	0		
		Arms	Equal	1.5		
			Unequal	0		
		Legs	Equal	1.5		
			Unequal	0		
			Total Score			

Canadian Stroke Scale was determined at the time of admission after 7 days Follow-up[23]

IV. Observation

Table No.1 : Symptoms of ICH patients at the time of admission.

Symptoms	**ICH Patients(n=100)**
Altered sensorium	92 (92%)
Headache	22 (22%)
Vertigo	42 (42%)
Vomiting	40 (40%)
Unsteadiness of gait	71 (71%)
Speech disturbances	76(76%)
Diplopia	23(23%)
Motor disturbances	88(88%)
Sensory disturbances	40 (40%)
Convulsion	16(16%)
Visual Blurring	10 (10%)
Others	1 (1%)

Table no.1 shows altered sensorium was common in 92 no. of patients (92%), followed by, motor disturbances 88 (88%), sensory disturbances 40 (40%).

Table No.2 : Neurological examination of ICH patients at the time of hospitalization.

NeurologicalExaminations	ICH Patients (n=100)
Hemiparesis/Hemiplegia	88 (88 %)
Speech disturbances	76(76%)
Cranial Nerve involvement	70 (70%)
Cerebellar Signs	10 (10%)
Nystagmus	10 (10%)
Quadriparesis	8(8%)

Table- 2 shows. The maximum no. of patients was found with hemiparesis/ hemiplegia, that is 88 (88%).

Table No.3 : Age Distribution.

Age Distribution	No. of Cases
21 – 30	2
31 - 40	1
41 – 50	5
51 - 60	14
61 - 70	58
71 -80	17
81 - 90	3

Table no. 3 shows age distribution of patients with maximum no of patients in age range 61- 70 years range may be due to more no of patients with risk factors like hypertension.

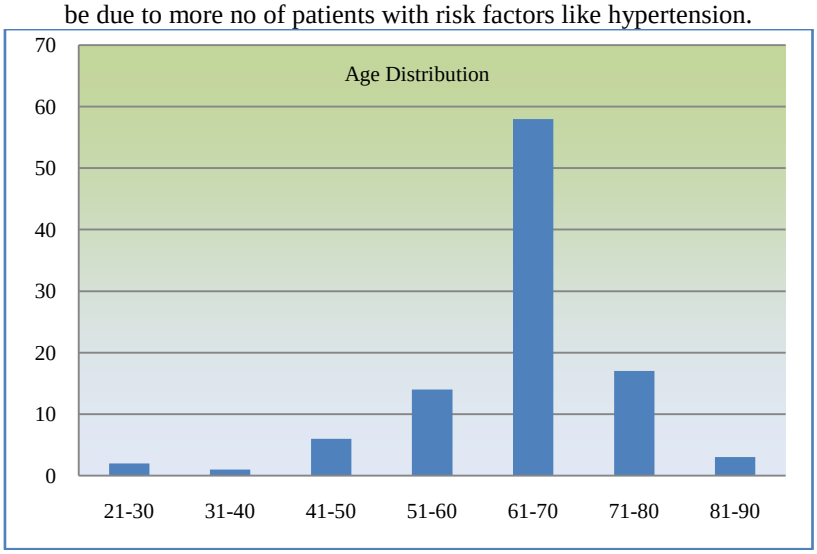

Table No.4: Sex distribution of ICH patients (N = 100).

Sex	N (=100)	Percent
Male	64	64
Female	36	36
	100	100 %

Table no.4 shows 64% male and 36% were female.

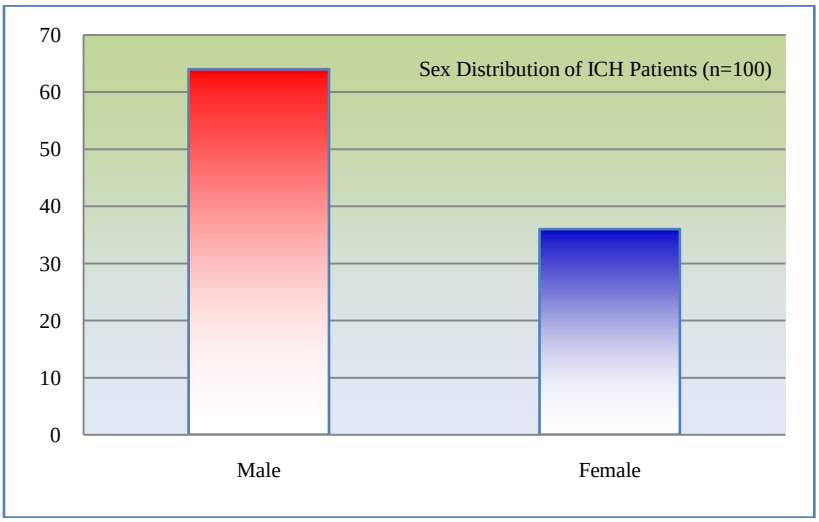

Table No.5 : Location of intracerebral hemorrhages:

Site	Location	ICH(N = 100)
Supratentorial	Basal Ganglia And Internal Capsule	50 (50 %)
	Thalamic	20 (20 %)
	Cortical	10 (10 %)
	Midbrain	2 (2 %)
Infratentorial	Cerebellum	10 (10%)
	Pons	6 (6 %)
	Medulla	2 (2 %)

Table No-5 shows maximum no of cases are basal ganglia and internal capsule areas.

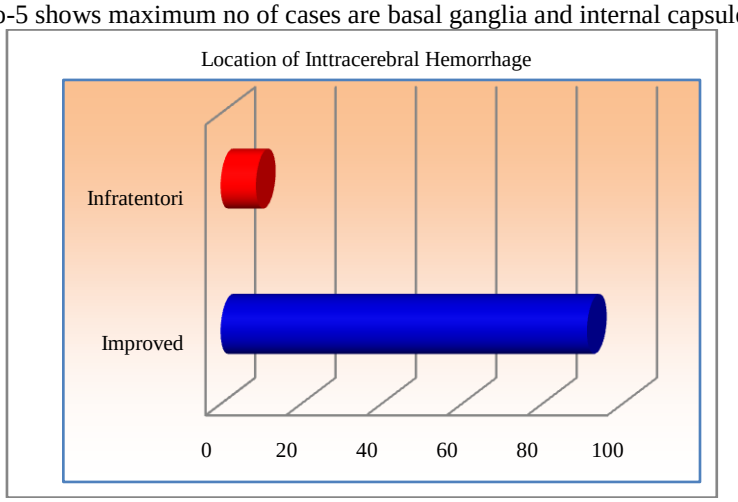

Table No.6 : Risk factors for ICH (n= 100)

Risk Factors	N= 100
Hypertension	65
Diabetes Mellitus	0
Both Diabetes Mellitus And Hypertension	35
AV Malformation	4
Anticoagulation	2
Past / Current Smoker	35
Alcoholic	15

AS shown in Table no.6 hypertension is the principal risk factor (65%) in ICH in this study.

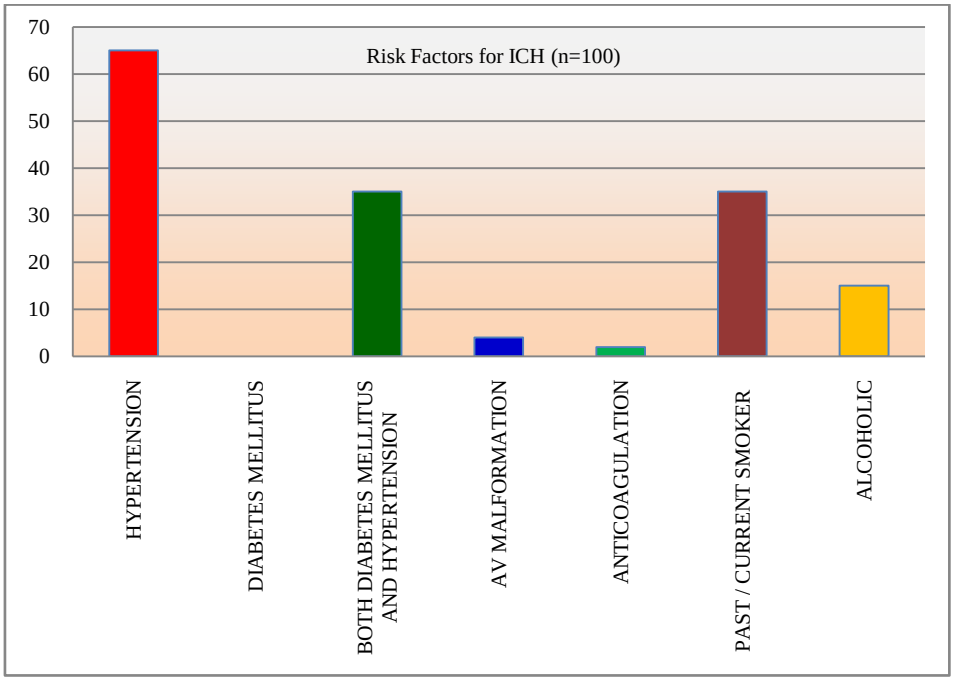

Table No.7 : GLASGOW comma scale (GCS) at the time of Admission.

GCS	No. (n=100)
< 8	80
9- 12	18
> 13 – 15	2

Table No-7 shows maximum number of patients were presented with GCS < 8 (80%).

Table No.8 : GLASGOW comma scale (GCS) at the Day 7.

GCS	No.	Mean ferritin (ng/ml)
Death	30	161.98
< 8	10	149.39
9 – 12	27	94.73
13 – 15	33	76.55

Table No-8 shows at day 7 mortality was 30%, patients with GCS < 8 was 10% and the GCS 9 – 12 was 27 % and GCS 13-15 was 33%. The mean ferritin level at admission who died was 161.98 ng/ml. The patients with GCS < 8 was 149.39 ng/ml and GCS 9 – 12 was 94.73 ng/ml and GCS 13 – 15 were 76.55ng/ml.

Table No.9 : Survivor & non-survivor at day 7.

	No of Cases (n=100)
Improved	**60**
Deteriorated	40

Table No.9 shows out of 100 patients on 7th day, 60 patients (60 %) improved and 40 (40 %) patients are deteriorated (or died).

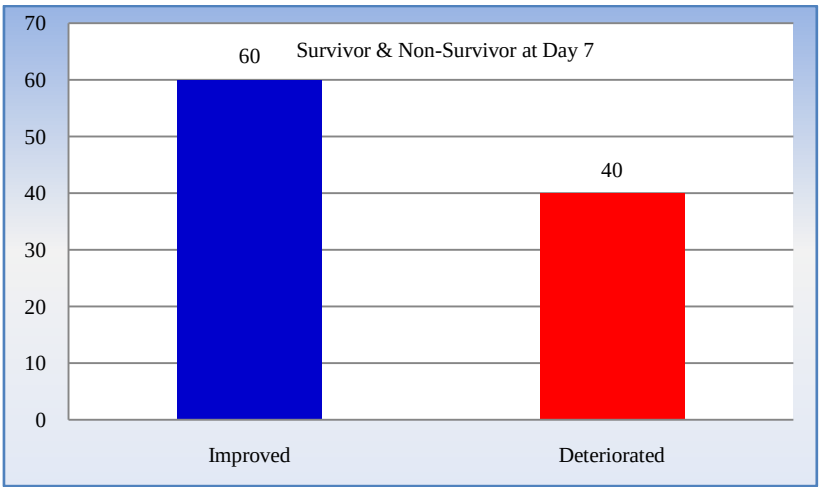

Table No.10 : Mean Canadian Stroke Scale (CSS) Score(At the time of Admission and Day 7).

Status of Patients	**Mean CSS at Admission**	**Mean CSS at Day 7**
Improve (60%)	2.59	4.58
Deteriorated (40%)	4.54	2.62

Patients who improved (60%) mean CSS score increased from 2.59 to 4.58, and the patient who decorated (40%) the mean CSS score decreased from 4.54 to 2.62.

Table No.11 : Mean ferritin level of patients who improved and deteriorated or dead.

	Mean Serum Ferritin(ng / ml)
Improved	79.20
Deteriorated	158.80

Patients who improved mean serum ferritin level was 79.20 ng/ml, and the patient who deteriorated the mean serum ferritin level was 158.80ng/ml.

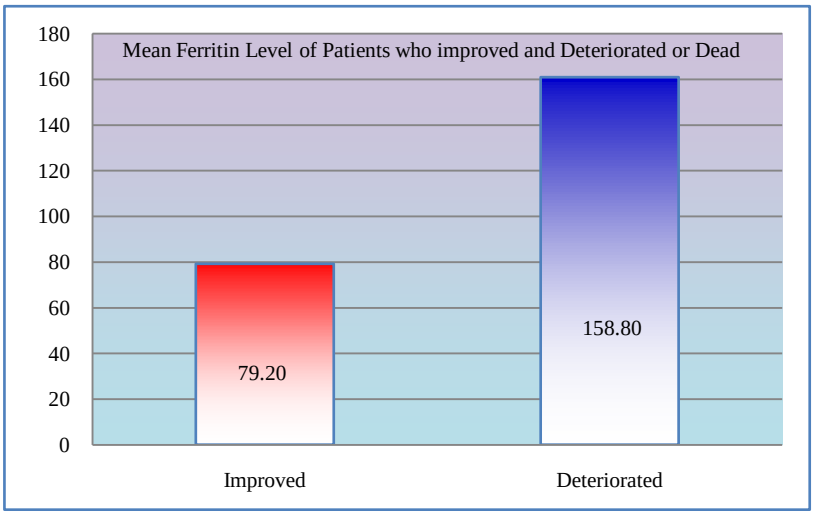

Table No.12 : Descriptive statistics of serum ferritin of patients of hemorrhagic stroke who improved.

MEAN	79.20
Median	67.25
Standard Deviation	36.76
Maximum	212.76
Minimum	34.44

Table No.13 : Descriptive statistics of serum ferritin of patients of hemorrhagic stroke who deteriorated.

MEAN	158.80
Median	98.78
Standard Deviation	56.77
Maximum	255.43
Minimum	46.66

Table No.14 : t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in hemorrhagic stroke.

	Improved	**Deteriorated**
Mean	79.20	158.80
Observation	60	40
Df	98	
t stat	7.68	
P(T <= t) two tail	0.0001	
t critical two tail	5.6758	

The above table shows that the significant different of mean serum level those who improved and deteriorated.

V. Discussion

In this study of 100 ICH patients of Intracerebral hemorrhage showing maximum number of patients was presented with altered sensorium (92%) followed by speech disturbances (76%), unsteady of gait (71%), sensory disturbances (40%), vertigo (42%), vomiting (40%), diplopia (23%), convulsion (16%). Similar findings were also found in studies conducted by Kora SA, Daddamani GB et al.[24]

While in studies by Kora SA, Daddamani GB et al,[24] the most common manifestation was altered sensorium (100%) in hemorrhagic strokes while in our study 92%. This may be due to high prevalence of cases of cerebellar and small ganglia capsular hemorrhage strokes in our study .

Neurological findings of the ICH patients showing maximum no of patients were with hemiplegia or hemiparesis (88%) followed by altered sensorium (65%), speech disturbances (76%), cranial nerve involvement (20%) and quadriparesis (8%). The minimum no. of patients was found with quadriparasis due to less no of patients in our study with brainstem hemorrhage.

Distribution of Intracerebral hemorrhage showing supratentorial location (82%) and infratentorial (18%). In supratentorial location maximum no of cases are at basal ganglia and internal capsule (50%) and followed by thalamic (20%), cortical (10%), and midbrain (2%). In infratentorial location maximum no. of patients haemorrhages are localized to cerebellum (10%) followed by pons (6%) and medulla (2%).

In our study out of 100 patients hypertension was the major risk factors (65%), followed by diabetes mellitus and hypertension combined (35%), but no case was found with only diabetes mellitus. This may be interpreted as diabetes mellitus when uncontrolled may predispose to atherosclerosis, nephropathy resulting hypertension .Four cases (4%) are young patients (<40 years). Common causes of young patients are AV malformation and anticoagulant warfarin.35% case are current or past smokers 15% are known alcoholic.

In this study at admission average GCS at the admission was 6 with < 8 GCS 80% and GCS 9 – 12 18% and GCS 13 – 15 was 2% , but at day 7, average GCS was 11 and no. of patients with GCS < 8, 9 – 12, 13 – 15 was 10% , 27% , 33% respectively .At day 7 no of patient died 30, which was similar to result of study conducted by R. Bhatia et al[26] in which mortality was 32.7%.

On admission mean CSS score was ~ 3 with maximum 7.5 and minimum 1.5. Out of 100 patients on day 7 ,60% patients improved that is mean CSS increased from 2.59 to 4.58 and 40% patient deteriorated that is mean CSS decreased from 4.54 to 2.62. This finding is consistent with study conducted by Narayan et al [28]Rajendran et al [27].

In comparison of mean serum ferritin level of improved group which was found 79.20 ng/ml , the mean ferritin level of those deteriorated was 158.80 ng/ml. Both values were lower than the mean value obtained in study Narayan et al [28] . This disparity may be due to subclinical iron deficiency due to nutritional deficiency in our patients. t-test assuming unequal variances to compared means of serum ferritin of improved and deteriorated groups in hemorrhagic stroke shows there is statistically significant difference in means of the two groups with $p < 0.005$. Hence mean serum ferritin in deteriorated group is significantly higher than those who improved.

VI. Summary

In our study 100 cases of intra cerebral hemorrhage diagnosed by CT scan of brain were studied during the period of December 2017 to December 2019..

The commonest clinical presentation was altered sensorium (92%). On neurological examination the most common finding was hemiplegia or hemiparesis (72%) and the minimum no of patients were found with quadriparesis (8%).

Supratentorial region is the commonest region of site for hemorrhagic stroke. In supratentorial location most common site is basal ganglia and internal capsule (50%). 18% cases were infratentorial and the most common site was cerebellum (10%).

Hypertension was the major risk factor (65%) followed by diabetes mellitus and hypertension combined (35%). 35% of cases current and past smokers and 15% were known alcoholic. In young stroke (< 40 years) most common causes were AV malformation and anticoagulation .

Mean GCS at the time of admission was 6 and with GCS < 8 was 80% and GCS 9 – 12 (20%) but the day 7 ,average GCS was 11 and no. of patients with GCS < 8, 9 – 12, 13 – 15 was 10% , 27% , 33% respectively. At day 7 mortality was 30%.

On admission mean CSS score was ~ 3. On day 7 , 60% patients were improved that is Mean CSS increased from 2.59 to 4.58 and 40% patient deteriorated that is mean CSS 4.54 decreased to 2.62.

Mean serum ferritin level of the group of patients improved was 79.20 ng/ml and those deteriorated was 158.80 ng/ml. t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in hemorrhagic stroke showed that there is statistically significant difference in means of the two groups with $p<0.001$. Mean serum ferritin in deteriorated patients is significantly higher than those who improved.

VII. Conclusion

- Admission level serum ferritin is associated with poor functional outcome of patients with acute hemorrhagic stroke at day 7.
- At admission level serum ferritin is a prognostic biomarker of acute hemorrhagic stroke.

References

[1]. WHO (1980) Bull. Who 58.113 -30.

[2]. JL Jameson, AS Fausi, D.L Kasner, SL Hauser, DL Longoria, J Loscalzo HARRISON's Principle of Internal Medicine 20th edition. New York: McGraw Hill Education 2018.

[3]. Pandian JD, Sudhan P. Stroke epidemiology and Stroke care service of India Journal of Stroke.2013;15(3) 128.

[4]. Dalal PM :Burden of Stroke: Indian Perspective ,International Journal of Stroke, 2006;1 (3) 164-166.

[5]. Marc Fisher MD, Bo Norrving. 1st Global Conference on Healthy lifestyles and Non-communicable diseases Control. Moscow, April 28-29, 2011.

[6]. Gupta R, Joshi P, Mohan V, Reddy S, Yusuf S. Epidemiology and causation of coronary heart disease and stroke in India. Heart 2008; 94:16-26.

[7]. CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods, and results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global burden of disease and risk factors .Washington DC :World bank and New york : OUP. P[45 -240 .]

[8]. American Stroke Association. Primary Prevention of Ischemic Stroke: A Guideline from the American Heart Association/ American Stroke Association Stroke Council. Stroke. 2006; 37: 1583-1633.

[9]. Stroke Unit Trialist's Collaboration. How do stroke units improve patient outcomes ? A collaborative systematic review of the randomized trials. Stroke 1997; 28: 2139-44.

[10]. Peter Langhorne, Linda de Villiers, Jeyaraj Durai Pandian. Applicability of stroke-unit care to low-income and middle-income countries Lancet Neurology 2012; 11: 341-48.

[11]. Strong K, Mathers C, Bonita R. Preventing stroke: saves lives around the world. Lancet Neurology 2007; 6:182-7.

[12]. Valery L. Feigin, Bo Norrving, George A. Mensah. Global Burden of Stroke AHA 2017.116.308413

[13]. Kameshwar Prasad,Deepti Vibha, Meenakshi : Cerebrovascular disease in South Asia ; PART – 1, JRSM Cardiovascular disease vol 1, 7 , 2012

[14]. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, Radhakrishnan K. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009 Apr;40(4):1212-8.

[15]. Feigin V, Lawes C, Bennet D, Barker_ Cello S, Parag V. Worldwide stroke incidence and early case fatality in 56 population based studies: a systematic review. Lancet Neurology 2009; 8 (4): 355-369

[16]. Bharucha N, Kuruvilla T. Epidemiology of stroke in India. Neurol J Southeast Asia 19

[17]. Pandian J et al. Public awareness of warning symptoms, risk factors and treatment of stroke in Northwest India. Stroke 2005; 36: 644-48.98; 3: 5-8.18
[18]. Wu J, Hua Y, Keep RF, Nakamura T, Hoff JT, Xi G. Iron and iron handling proteins in the brain after intracerebral hemorrhage. Stroke. 2003;34(12):2964–9.
[19]. Wang J, Doré S. Heme oxygenase-1 exacerbates early brain injury after Intracerebral haemorrhage. Brain. 2007;130(6):1643–52.
[20]. Deane R, Zheng W, Zlokovic BV. Brain capillary endothelium and choroid plexus epithelium regulate transport of transferrin-bound and free iron into the rat brain. J Neurochem. 2004;88(4):813–20.
[21]. Wagner KR, Sharp FR, Ardizzone TD, Lu A, Clark JF. Heme and iron metabolism & colon; role in cerebral hemorrhage.J Cereb Blood Flow Metab. 2003;23(6):629–52.
[22]. Connor JR, Menzies SL. Cellular management of iron in the brain. J Neurol Sci. 1995;134:33–44.
[23]. Qian ZM, Morgan EH. Changes in the uptake of transferrin-free and transferrin-bound iron during reticulocyte maturation in vivo and in vitro.Biochem BiophysActa. 1992;1135(1):35–43.
[24]. Cote R, Hachinski VC, Shurvell B, Norris JW, Wolpson C (1986).The Canadian neurological Scale: a preliminary study in acute stroke. Stroke 17:731–737.
[25]. Kora S.A, Doddamani G.B, Goorannavar S.M, Biradar Satish. Journal of clinical and diagnostic research 2011 April, vol- 5(2) : 217-221.
[26]. R.B. Libman, T.G. Kwiatkowski, M.D. Hansen et al; Differences between Anterior and Posterior Circulation Stroke in TOAST, Cerebrovascular Diseases, 2001; 11: 311-6.
[27]. Rohit Bhatia, Hariom Singh, Madakasira V Padma, Kameshwar Prasad, Manjari Tripathi, Guresh Kumar, Mamta Bhusan Singh. A prospective study in-hospital mortality and discharge outcome in spontaneous Intracerebral hemorrhage. 2013; 61: 244-8.
[28]. SR Rajendran, S Periswami, MT Manjuladevi, N George : Evaluation of serum ferritin as a prognostic marker in acute hemohhragic stroke. J Neuroscience Rurlapract. 2019.
[29]. M. Narayan, SK Singh : Study of Association between serum ferritin and prognosis of patients in acute ischemic and hemorrhagic stroke : IOSR-JDMS, 2279-0853. Vol.17, 2018.

S.C. Singh, et. al. "A Prospective Study to Determine Serum Ferritin as a Biomarker for Prognosis of Patients with Acute Hemorrhagic Stroke." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(09), 2021, pp. 49-59.