Evaluation of serum ferritin as prognostic marker in acute hemorrhagic stroke

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Abstract-Acute neurological dysfunction caused by a stroke or cerebrovascular accident can have either an ischemic or hemorrhagic cause. A blood artery rupture that results in bleeding into the brain causes hemorrhagic stroke. There are two types of hemorrhagic stroke: subarachnoid haemorrhage (SAH), and intracerebralhaemorrhage (ICH) which is more prevalent, . High mortality and significant morbidity are linked to hemorrhagic stroke[1]. Serum ferritin levels were one of 61 independent predictive molecular biomarkers evaluated in the immediate phase following a hemorrhagic stroke that could predict motor functional recovery[2]. The goal of this study was to identify the serum ferritin level at admission time as a predictive prognostic biomarker in acute hemorrhagic stroke. This cross-sectional observational study was conducted on 72 patients hospitalised to the medical intensive care unit between October and December in a single institution.72 patients who were admitted to the medical ICU between October 2020 and March 2022 for their first episode of stroke and who were clinically and radiologically determined to have primary intra cerebral haemorrhage were included in this single-center, hospital-based, cross-sectional observational study. The study participants were divided into three groups according to their mRS scores: those with a good prognosis (mRS = 0-2), those with a poor prognosis (mRS = 3-5), and those with the worst prognostic outcome of death (mRS = 6). Also, patients were divided into three groups according to the GCS Score change: better, deteriorated, and died. In addition to being compared between research groups, ferritin levels were also linked to ICH severity indices. Low GCS and high mRS scores were related with high serum ferritin concentrations, indicating the severity of the stroke.

Introduction:Acute neurological dysfunction caused by a stroke or cerebrovascular accident can have either an ischemic or hemorrhagic cause. A blood artery rupture that results in bleeding into the brain causes hemorrhagic stroke. There are two types of hemorrhagic stroke: subarachnoid haemorrhage (SAH), which is more prevalent, and intracerebralhaemorrhage (ICH). Stroke caused by haemorrhage is known to have high death rates and significant morbidity. [1] Early detection and treatment are crucial because bleeding typically spreads quickly, abruptly impairing consciousness and leading to neurological impairment. 10% to 20% of strokes per year are hemorrhagic strokes. In the United States of America, the United Kingdom, and Australia, bleeding occurs in strokes at a rate of 8–15%, whereas in Japan and Korea, it occurs at a rate of 18–24%. The incidence ranges from 12% to 15% of cases per 1,00,000 per year.Asians and people from low- and middle-income nations are particularly affected. Risk factors that can be changed include high blood pressure, smoking, drinking too much alcohol, having low levels of low-density lipoprotein cholesterol, having low levels of triglycerides, and using medications including sympathomimetics, anticoagulants, and antithrombotic agents. Non-modifiable risk variables include elderly age, male sex, CVA, and Asian ethnicity[3-4]. In addition to clinical diagnosis, radio imaging, particularly brain computed tomography (CT), is essential for the diagnosis and prognosis of ICH. Some of the first indicators of ICH include clinical indications like loss of consciousness as defined by the Glasgow Coma Scale (GCS), blood pressure (BP) indices, and radiological markers including size, location, and extent of ICH, surrounding edoema, and haemorrhageextension[5].The modified Rankin scale (mRS), a stroke grading method that has received substantial validation, may be used to systematically determine the long-term stroke outcome and functional disability[6]. Coma, big hematoma with volume larger than 30 ml, intraventricularhaemorrhage, posterior fossa haemorrhage, elderly age greater than 80 years, hyperglycemia, and chronic renal disease are the unfavourable prognostic factors . The main issues with ICH include early deterioration and mortality. At the time of the presentation, the patient's coma indicated a dire prognosis. Due to their wide range of applications in the last few decades, molecular biomarkers in stroke have drawn the attention of clinicians all over the world. These applications include making diagnosis easier, characterising clinical size and severity, determining long-term prognosis, and choosing the best course of treatment. [7].Moreover, neuroimaging biomarkers (such as computed tomography and magnetic resonance imaging), which are often utilised after brain damage, are only able to shed light on the systemic physiological processes behind brain healing. [7]The combination of molecular biomarkers and clinical severity or neuroimaging findings has been leading to increased prognostic accuracy for motor functional recovery after stroke, which may help clinicians identify the individuals who are most susceptible to the worst short- and long-term functional prognosis after injury and ensure that they receive the appropriate amount of rehabilitation

to maximise outcome after stroke since they were moved from an intensive care unit. [8] The amount of serum ferritin is a marker for the body's iron reserves and is frequently used for laboratory diagnosis of iron excess and deficient diseases.The potential involvement of serum ferritin in foretelling the iron-mediated free radical damage in the pathophysiology of cardiovascular illnesses has recently been examined by a number of researchers.

AIM AND OBJECTIVES

AIM:To study the clinical presentation of patients with acute hemorrhagic stroke and to determine the association of serum ferritin level and functional outcome of patient.

Objectives:

1. **To study the clinical presentation of patients with respect to the presenting symptoms, neurological examination, location of hemorrhage and associated risk factors.**
2. **To estimate serum ferritin in patients with acute hemorrhagic stroke.**
3. **To determine association of serum ferritin level at the time of admission with functional outcome of patients with acute hemorrhagic stroke at day 7 of hospitalization.**

To establish the role of serum ferritin as a bio marker of severity and prognosis of acute hemorrhagic stroke.

Materials and Methods:The trial comprised 72 individuals who had their first episode of stroke between October 2020 and March 2022 and had been clinically and radiologically diagnosed with primary intra cerebral haemorrhage. Patients hospitalised to the department of medicine with acute hemorrhagic stroke within 48 hours after the beginning of symptoms and meeting the following criteria were chosen for the cross-sectional observational research.

Inclusion criteria:

Patients of either sex more than 18 years old,Patients presenting within 48 hours of onset of symptoms,Diagnosis of acute haemorrhagic stroke confirmed by non contrast CT scan of brain.

Exclusion criteria:

Patients with ischemic stroke,Patients with intraventricular and subarachnoid haemorrhage,Patients with body temperature greater than 37.5℃,Patients with infection,Patients with malignancy,Patients with liver diseases,Patients with anaemia,Patients with autoimmune disorders.

Functional outcome of patients:At the seventh day of hospitalisation, a prognostic evaluation was performed, which included a thorough physical examination, GCS assessment, and the recording of mRS scores. Depending on the degree of functional handicap following the

stroke, the individuals' mRS ranged from 0 (excellent health) to 6 (death). The research participants were divided into three groups according to their mRS scores: those with a favourable prognosis (mRS = 0-2), those with a poor prognosis (mRS = 3-5), and those with the worst prognostic outcome of death (mRS = 6). Also, patients were divided into three groups according to the GCS Score change: better, worsened, and died. In addition to being compared between research groups, ferritin levels were also linked to ICH severity indices.

Statistical analysis:Using the statistical programmeGraphPad Prism Version 8.4.3, the data was examined. Frequencies, means, medians, interquartile ranges, and standard deviations were used to give descriptive information. Depending on the kind of data, whether parametric or non-parametric, inferential statistical techniques such as one-way analysis of variance and Kruskal-Wallis tests were employed to compare serum ferritin and other parameters among the research groups. Any meaningful correlations between serum ferritin levels and ICH severity indicators were found using Spearman's correlation. Significant data was defined as a p-value less than 0.05.

Observation and Results

At the patient wards and intensive care unit of the Krishna Institute of Medical Sciences and Research hospital in Karad, this cross-sectional observational study was carried out. According to the study's inclusion and exclusion criteria, 103 patients in total were screened. The current study included 72 participants.

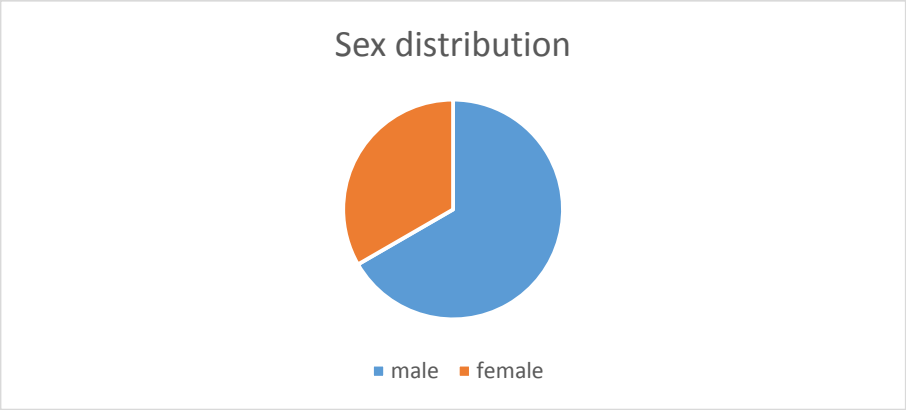
Table 1: Demographic and baseline characteristics (n=72)

Variable	Mean	Standard deviation(±)
Age	63.16	10.24
GCS on admission	7.47	1.94
GCS on day 7	8.75	4.45
mRS score on day 7	3.35	2.04
Ferritin on day of admission	233.79	122.89
Serum ferritin on day 7	227.41	127.04

SD- Standard deviation

Table 2:Demographic and baseline characteristics

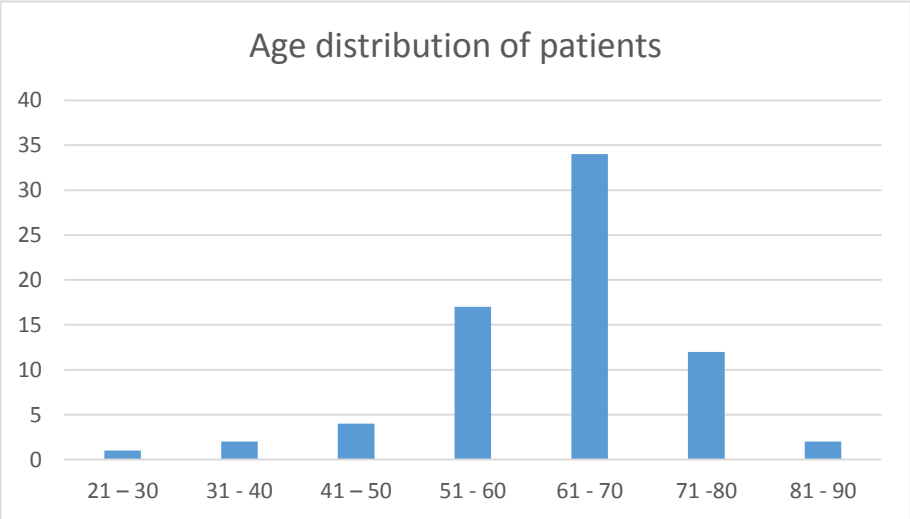
Variable	
Male: Female ratio	2:1
Glasgow Coma Scale on admission (Median)	7.5



Male female ratio is 2:1 among study population.48 male patients and 24 female were included in the study.

Table 3: Frequency distribution for age in study population

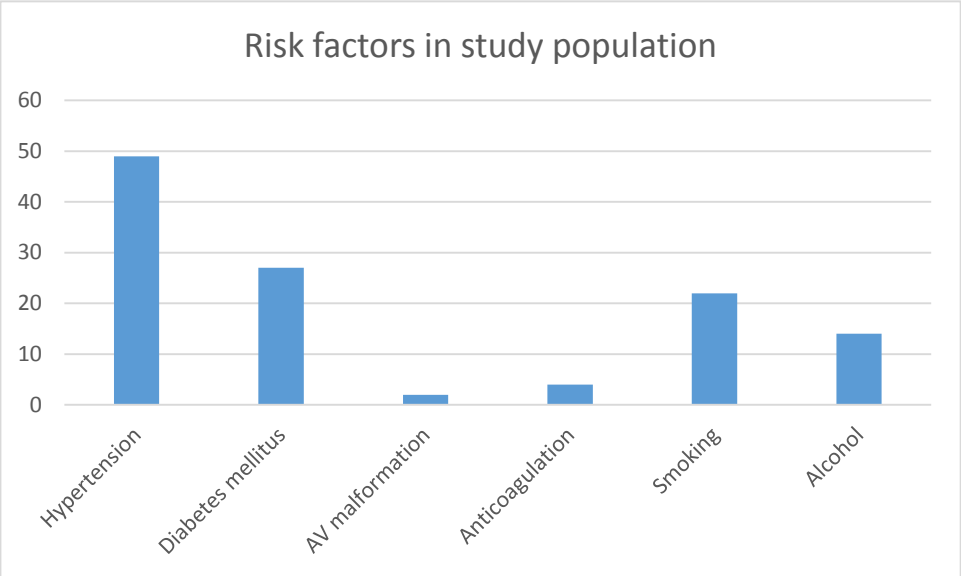
AGE DISTRIBUTION	n = 72(%)
21 – 30	1 (1.39)
31 - 40	2 (2.78)
41 – 50	4 (5.55)
51 - 60	17 (23.61)
61 - 70	34 (47.22)
71 -80	12 (16.66)
81 - 90	2 (2.78)



Age distribution of patients with maximum number of patients being in age range of 61- 70 years range may be due to more no of patients with risk factors like hypertension. Whereas minimum number of patients are found in the age range of 21 -30 years of age.

Table 4: Number of patients having risk factors for acute haemorrhagic stroke

RISK FACTORS FOR Intra Cerebral hemorrhage	n = 72(%)
Hypertension	49(68.05)
Diabetes mellitus	27 (37.5)
AV malformation	2 (2.78)
Anticoagulation	4 (5.55)
Smoking	22(30.55)
Alcohol	14(19.44)

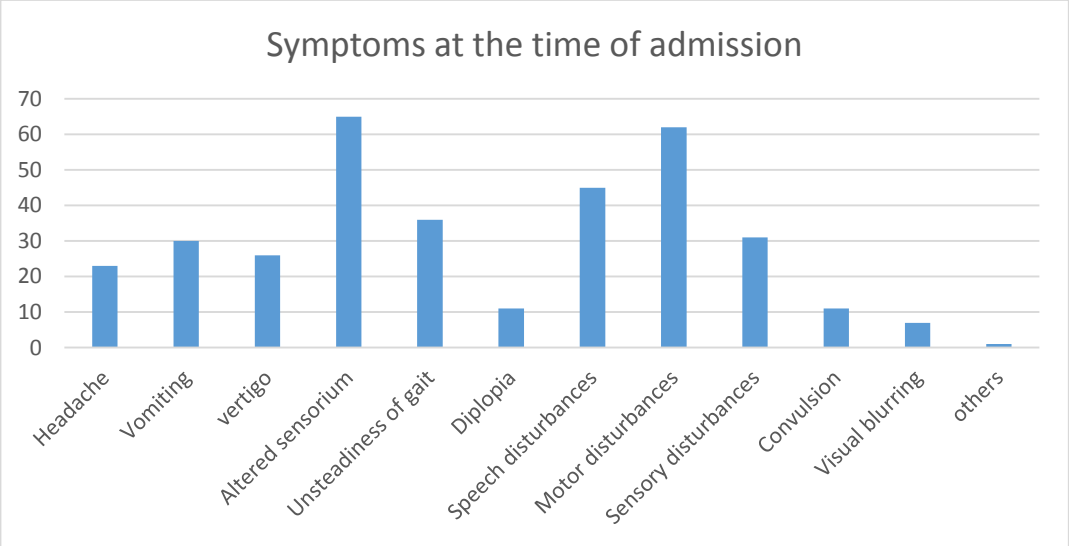


Hypertension is the principal risk factor in 49(68%)patients of ICH in this study as compared to ischemic stroke where atherosclerosis is the main risk factors either due to hypertension or diabetes mellitus or both. Diabetes Mellitus was reported by 27(37%) of the cases and 2(2%) patients had other rare risk factors like AV malformation and 4(6%) cases were on anticoagulant drugs like warfarin. Also 22(30%) patients were having history of smoking and 14(19%) patients were known alcoholic.

Table 5: Presenting symptoms at the time of admission

SYMPTOMS AT THE TIME OF ADMISSION	n = 72(%)
Headache	23 (31.94)
Vomiting	30 (41.67)
vertigo	26 (36.11)
Altered sensorium	65 (90.28)
Imbalance of walking	36 (50)

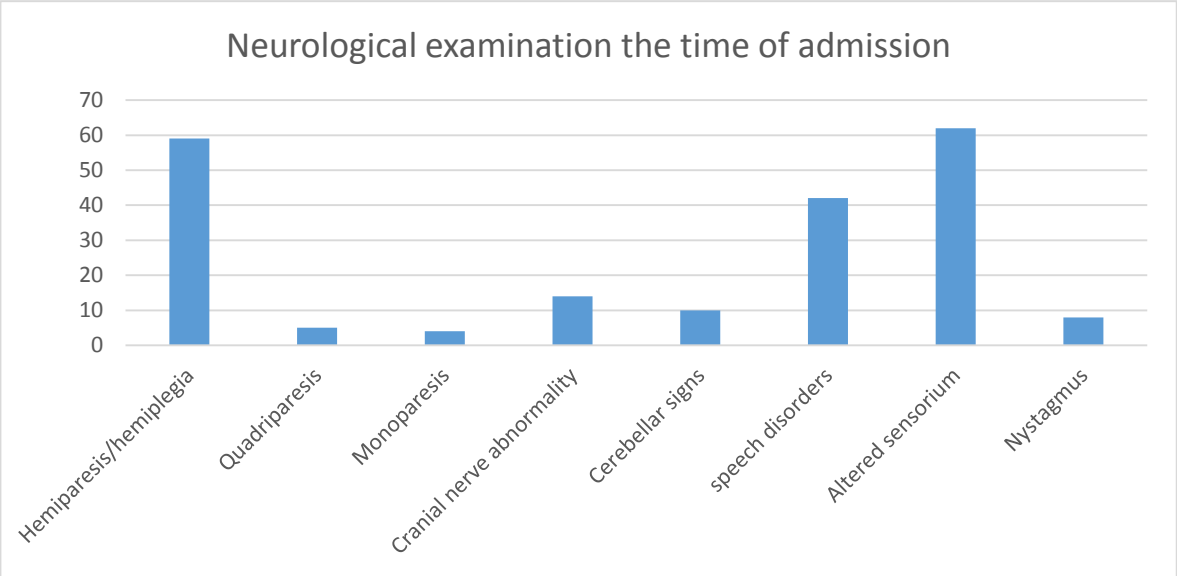
Diplopia	11 (15.28)
Speech disturbances	45 (62.5)
Motor disturbances	62 (86.11)
Sensory disturbances	31 (43.06)
Convulsion	11 (15.28)
Visual blurring	7 (9.72)
others	1 (1.39)



Of total 72 patients with hemorrhagic stroke maximum no. of patients was presented with altered sensorium 65(90%), followed by motor disturbances 62(86%), speech disturbances 45(62%), Imbalance of walking 36(50%), sensory disturbances 31(43%), vertigo 26(38%), vomiting 30(41%), diplopia 11(15%), headache 23(32%) and convulsion 11(15%).

Table 5: Neurological examination at the time of admission

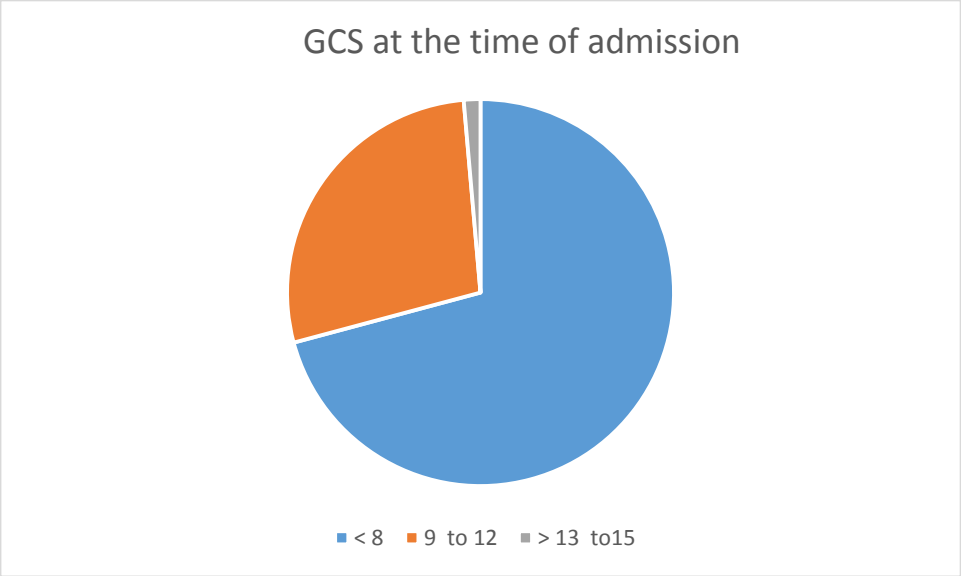
Neurological examination the time of admission	n = 72(%)
Hemiparesis/hemiplegia	59 (81.94)
Quadriparesis	5(6.94)
Monoparesis	4 (5.55)
Cranial nerve abnormality	14 (19.44)
Cerebellar signs	10 (13.89)
speech disorders	42 (58.33)
Altered sensorium	62 (86.11)
Nystagmus	8(11.11)



Neurological examinations of the 72 patients with hemorrhagic stroke Patients at the time of admission,The maximum no. of patients was found with altered sensorium that is 62 (86%), followed by hemiparesis or hemiplegia 59(82%), speech disorders 42(58%), cranial nerve abnormality 14(19%) and quadriparesis 5(7%).

Table 6: Glasgow Coma Scale at the time of admission

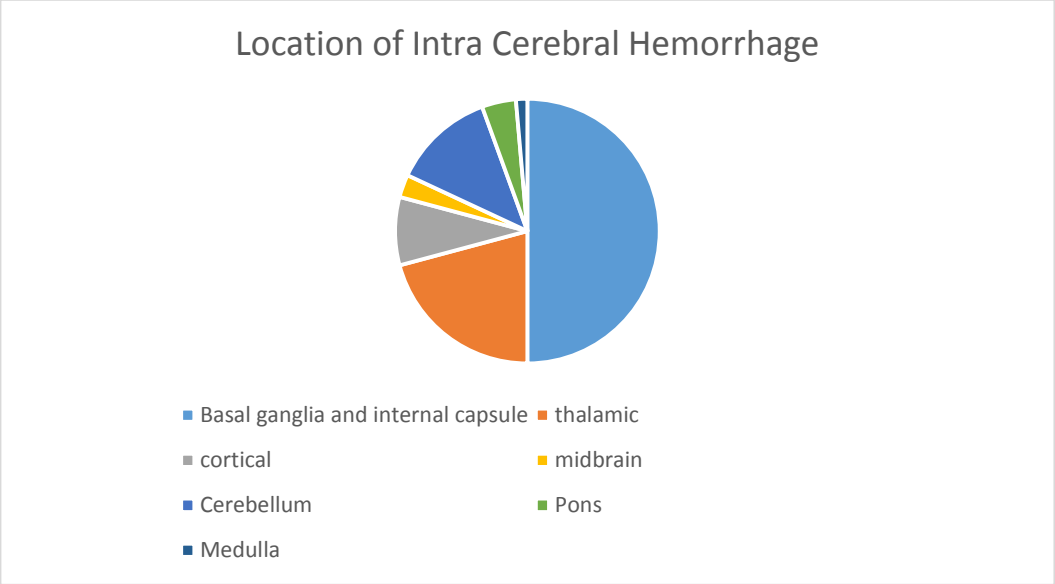
Glasgow Coma Scale	n = 72(%)
< 8	51 (70.83)
9- 12	20 (27.78)
> 13 – 15	1 (1.39)



Of total 72 patients with hemorrhagic stroke maximum number of patients 51(71%) presented with Glasgow Coma Scale < 8, 20(28%) patients presented with Glasgow Coma Scale 9-12,1(1%)patient presented with Glasgow Coma Scale >13-15.

Table 7: Location of Intra Cerebral Haemorrhage

Location of Intra Cerebral Haemorrhage		**n=72(%)**
Supratentorial	Basal ganglia and internal capsule	36 (50%)
	thalamic	15 (20.83)
	cortical	6 (8.33)
	midbrain	2 (2.78)
Infratentorial	Cerebellum	9 (12.5)
	Pons	3 (4.17)
	Medulla	1 (1.39)



Of total 72 patients with hemorrhagic stroke in maximum number of cases the location of haemorrhage is supratentorial 59(82%) out of which 36(50%) cases shows haemorrhage in basal ganglia internal capsule areas, 15(20%) cases in thalamic and 6(8%) cases are cortical site, and 2(3%) cases are in midbrain. Number of case having infratentorial bleeds are 13(18%), out of which 9(13 %) are in cerebellum,3(4%)cases shows haemorrhage in pons,1(1%)cases shows haemorrhage in medulla.

Comparison of parameters between the patients having good prognosis, bad prognosis and those who died on 7th day of hospitalization

Variable	Good prognosis (mRS = 0–2) (n = 34)	Bad prognosis (mRS = 3–5) (n = 20)	Death (mRS = 6) (n = 18)	P-value
Age (mean ± SD)[1]	57.41± 9.97*$^{\#}$	64.10 ± 6.81$^{\#\$}$	73 ± 4.88*$^{\$}$	<0.0001
GCS on admission [Median(IQR)][2]	9(8-10)*$^{\#}$	6(6-7.75)$^{\#\$}$	5(5-6)*$^{\$}$	<0.0001
Serum Ferritin on Admission (mean ± SD)[1]	140.4 ± 62.59*$^{\#}$	290.6 ± 111.0$^{\$}$	347 ± 82.88$^{\$}$	<0.0001
Serum Ferritin on day 7 of hospitalization (mean ± SD)[1]	124.3 ± 55.77*$^{\#}$	290.6 ± 104.2$^{\#\$}$	352.1 ± 82.18*$^{\$}$	<0.0001

mRS- Modified rankin scale

1-One-way ANOVA followed by post hoc Tukey's test, 2- Kruskal Wallis test followed by post hoc Dunn's test

* Statistically significant as compared to patients who deteriorated, # Statistically significant as compared to patients who died, $ Statistically significant as compared to patients who improved

P value < 0.05 considered statistically significant

Comparison of parameters between the patients showing improvement or deterioration in Glasgow Coma Scale score on 7th day of hospitalization

Variable	Improved (n=40)	Deteriorated (n=14)	Died (n=18)	P-value
Age (mean ± SD)[1]	57.95± 9.72*#	65.43 ± 5.91#$	73 ± 4.88*$	<0.0001
GCS on admission [Median(IQR)][2]	8.5(8-10)*#	6(6-7)$	5(5-6)$	<0.0001
Serum Ferritin on Admission (mean ± SD)[1]	150.6 ± 68.44*#	325.9 ± 106.1$	347 ± 82.88$	<0.0001
Serum Ferritin on day 7 of hospitalization (mean ± SD)[1]	134.3 ± 64.28*#	333.2 ± 81.52$	352.1 ± 82.18$	<0.0001
mRS [Median(IQR)][2]	2(1-2)*#	5(4-5)$	6(6-6)$	<0.0001

mRS- Modified rankin scale

1-One-way ANOVA followed by post hoc Tukey's test, 2- Kruskal Wallis test followed by post hoc Dunn's test

* Statistically significant as compared to patients who deteriorated, # Statistically significant as compared to patients who died, $ Statistically significant as compared to patients who improved

P value < 0.05 considered statistically significant

Mean ferritin level of patients who improved compared to those who deteriorated or died

	Patients who improved(n=40)	Patients who deteriorated or died(n=32)	P- Value
Mean Serum Ferritin (ng/dl) on admission	150.6(68.44)	337.8(92.74)	<0.0001
Mean Serum Ferritin (ng/dl) at day 7	134.3(64.28)	343.8(81.12)	<0.0001

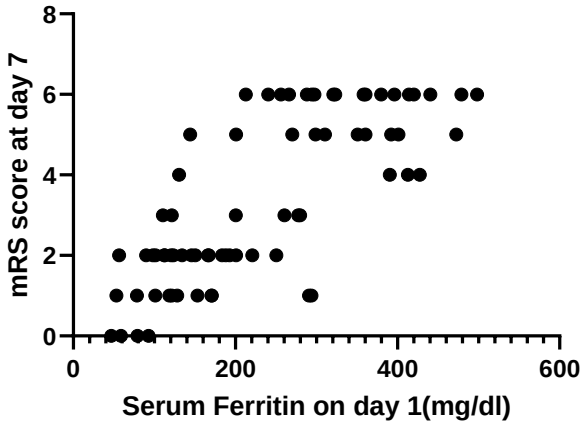
Unpaired t test used. P value < 0.05 considered statistically significant

Correlation of Ferritin level on day 1 with the Severity indices at 7th day

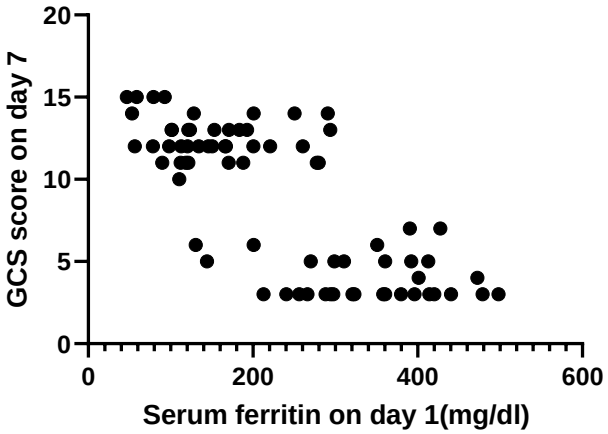
Severity Indices	Spearman Coefficient	95% CI	P - value
mRS	**0.7561**	**0.6316 to 0.8426**	**<0.0001**
GCS	**-0.7096**	**-0.8108 to -0.5673**	**<0.0001**

correlation of serum ferritin on day 1 with the severity indices on 7th day like mRS and Glasgow Coma Scale score. It was found that serum ferritin level shows positive correlation with mRS score on day 7 and negative correlation with GCS score on day 7 were shown in figures below.

Correlation between serum ferritin on day 1 and modified Rankin Scale score on day 7



Correlation between serum ferritin on day 1 and Glasgow Coma Scale score on day 7

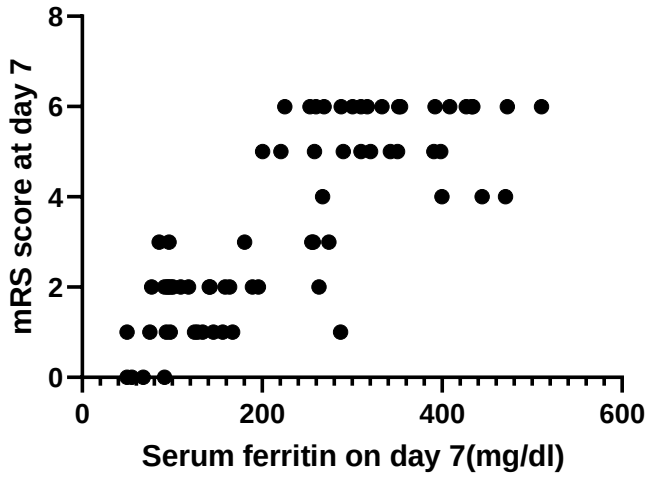


Correlation of Ferritin level day 7 with the Severity indices at 7th day

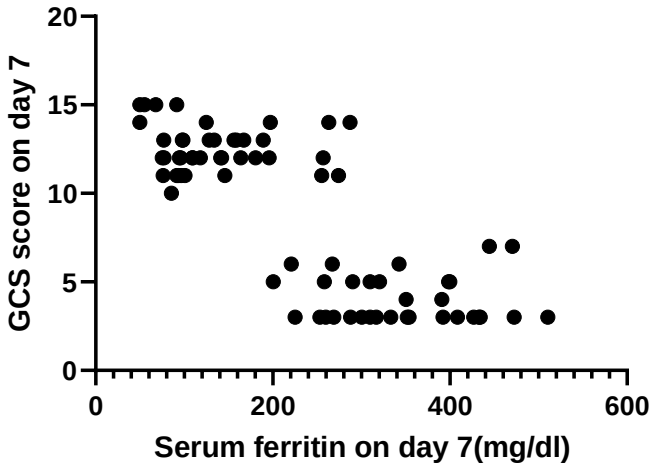
Severity Indices	Spearman Coefficient	95% CI	P - value
mRS	**0.7930**	**0.6840 to 0.8674**	**<0.0001**
GCS	**-0.7346**	**-0.8279 to -0.6016**	**<0.0001**

correlation of serum ferritin on day 7 with the severity indices on 7th day like mRS and GCS score. It was found that serum ferritin level shows positive correlation with mRS score on day 7 and negative correlation with GCS score on day 7 were shown in figures below.

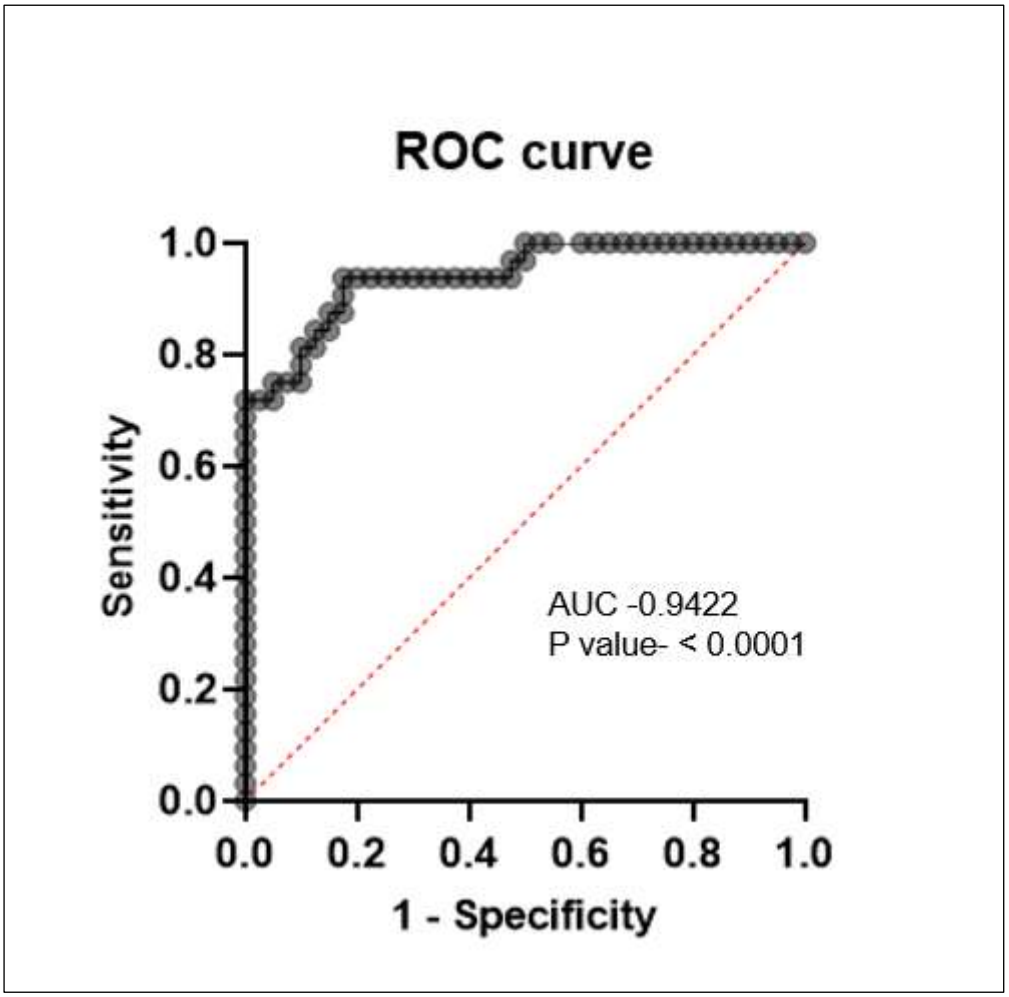
Correlation between serum ferritin on day 7 and mRS score on day 7



Correlation between serum ferritin on day 7 and GCS score on day 7



Receiver operating characteristic curve of baseline serum ferritin with area under the curve (AUC) for predicting poor prognosis.



AUC- Area under curve

Logistic regression analysis showed baseline serum ferritin as an independent predictor of death or deterioration in acute hemorrhagic stroke. A unit increase in serum ferritin increases the odds of death or deterioration by 2.4% (P<0.0001).The area under the curve of the receiver operator characteristic (AUROC) of baseline serum ferritin for predicting poor prognosis was 0.9422 (95% CI:0.8913 to 0.9931, P<0.0001) with sensitivity of 87.5% and specificity of 85% when the cut-off serum ferritin was 230.7

Conclusion:The goal of the current cross-sectional investigation was to determine if serum ferritin and the outcome of acute hemorrhagic stroke were related. It was shown that patients with greater serum ferritin levels experienced acute hemorrhagic strokes that were more severe and had worse outcomes after a week. Acute hemorrhagic stroke scores and serum ferritin levels were shown to be positively correlated in the current study, showing a worse prognosis for patients with greater serum ferritin levels. Low Glasgow Coma Scale (GCS), a measure of the severity of the stroke, was

likewise correlated with high serum ferritin concentrations. Acute hemorrhagic stroke mortality and worsening were both independently predicted by serum ferritin, according to regression analysis. Hence, serum ferritin may serve as a predictive indicator for acute hemorrhagic stroke.It was recommended that all patients with acute hemorrhagic stroke should have their serum ferritin levels checked in addition to their clinical, laboratory, and imaging results in order to predict how well they would recover.

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