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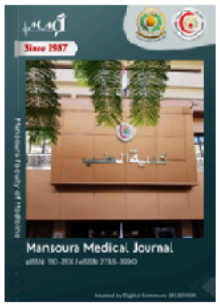

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Role of Serum Ferritin and D-Dimer on Short Term Outcome in Acute Ischemic Stroke

Nourhan Ahmed Galal Sadek

Neurology Department, Faculty of medicine, Mansoura University, Egypt, nora0galal@gmail.com

Mohammed Mahmoud Abbas Ali

Neurology Department, Faculty of medicine, Mansoura University, Egypt

Yousra Mahmoud Amin Tera

Clinical Pathology Department, Faculty of medicine, Mansoura University, Egypt

Mohamed Abd-El-Salam Mohamed Ali

Neurology Department, Faculty of medicine, Mansoura University, Egypt

ORIGINAL STUDY

Role of Serum Ferritin and D-dimer on Short-term Outcome in Acute Ischemic Stroke

Norhan Galal [a,*], Mohammed Abbas [a], Yousra Tera [b], Mohamed Abdelsalam [a]

[a] Neurology Department, Faculty of Medicine, Mansoura University, Egypt
[b] Clinical Pathology Department, Faculty of Medicine, Mansoura University, Egypt

Abstract

Background: **Acute ischemic stroke (AIS) has been considered as a main reason of death globally. Currently, intervention could significantly enhance outcomes and reduce disability. Studies have been conducted to determine the factors that may have a role in the context of AIS prognosis formulation. Prognostic indicators, that has gained great clinical interest recently, are serum ferritin and D-dimer (DD).**

Aim: **The aim of the current study was to assess the relation between serum levels of both ferritin and DD and severity of AIS at time of presentation and its relationship with the short-term outcome of patients.**

Methods: **The present study was an observational prospective study with analytic component that was carried out on 100 patients. All patients were subjected to measuring severity of stroke using National Institute of Health Stroke Scale (NIHSS) score at time of admission and 5 days later for short-term outcome and measuring of serum level of both D-dimer and ferritin on admission. Size of infarction on CT was determined by multiplying area of infarction by number of CT slices and slice thickness. Ischemic infarction size >1.5 cm was categorized as large vessel infarction.**

Results: **There was statistically significant positive correlation between NIHSS initial and NIHSS at follow-up with serum ferritin and D-Dimer. There was statistically significant correlation between serum ferritin level and CT brain results as regard small and large vessel infarction with higher median ferritin is detected among cases with large vessel than small vessel disease. There was statistically significant relation between D-dimer level and CT brain results ($P < 0.05$) with higher d-dimer among cases with large vessel than small vessel diseases.**

Conclusion: **Elevated plasma DD levels and serum ferritin were significantly accompanied by poor short-term outcome, determined by NIHSS follow-up, suggesting the potential role of plasma DD and serum ferritin levels as predictive markers for short-term poor outcomes in cases with AIS. Both serum ferritin and D-dimer levels were significantly associated with large vessel occlusion determined by CT.**

Keywords: Acute ischemic stroke, D-dimer, National Institute of Health Stroke Scale, Serum ferritin

1. Introduction

Stroke is a syndrome consisting of rapidly developing clinical manifestations of focal or global disturbance of brain functions lasting for at least 24 h or leading to death with no evident etiology other than a vascular origin (Feigin et al., 2018). Stroke is the second most frequent cause of mortality and third most frequent cause of disability all over the world (Fure et al., 2005). Worldwide, 68% of strokes are ischaemic and 32% are hemorrhagic (Lozano et al., 2012).

In recent years, about 3.5% of total healthcare expenditures in Western nations are spent on stroke (Benjamin et al., 2017). Severe strokes with disability more than 20 on NIHSS cost twofold as much as mild strokes, in spite of comparable diagnostic testing (Brott et al., 1989).

The worldwide burden of disease study 2013 demonstrated an increase in stroke risk and

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* Corresponding author at: Neurology Department, Faculty of Medicine, Mansoura University, Egypt. Fax: 0502214839.
E-mail addresses: norhangalal@mans.edu.eg, nora0galal@gmail.com (N. Galal).

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disability adjusted life years in younger adults aged 20–64 years (Struijs, 2006). Such increase is predominant in developing countries and with greater possibility of disability among cases with lower education. Biomarkers are objective indicators utilized to evaluate normal or pathologic processes, assess responses to medical interventions, and predict outcomes (Go et al., 2014). A few blood biomarkers are utilized to support clinical judgments. For instance, high-sensitive cardiac troponin T guides the diagnosis of myocardial infarction (MI) and B-type natriuretic peptide (BNP) is utilized to evaluate heart failure, and C-reactive protein values indicate the response to antibiotics in bacterial infection. Serum ferritin is an appropriate index of the amount of cellular iron stores and, as a result, could be associated with the availability of iron in the infarcted cerebral tissue (Krishnamurthi et al., 2015).

D-dimer, which is produced by the actions of thrombin, factor XIIIa, and plasmin, is a marker of intravascular fibrin breakdown. Major thromboembolic events are successfully excluded by low plasma D-dimer concentrations, but high concentrations are linked to a number of illnesses, such as deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), atrial fibrillation (AF), stroke, and malignant tumours (Kamtchum-Tatuene and Jickling, 2019). So, we conducted this study to assess the relation between serum levels of both ferritin and D-dimer and Severity of AIS at time of presentation and its relationship with the short-term outcome of cases.

2. Patients and methods

This was an observational prospective study with analytic component and carried out for one year after approval of the Institutional Review Board (IRB). This study included patients attending the Neurology department at Mansoura University presenting with AIS. This study includes cases more than 18 years, from both genders, diagnosed with CT scan within 48 h of onset of symptoms and with NIHSS Score ranging from (5–15). But in this study, we ruled out patients who refused to contribute to the study, patients were not fulfilling inclusion criteria, patients with history of new infection or inflammation one month before the onset of symptoms, patient with history of malignancy/DVT/Pulmonary Embolism/peripheral vascular diseases and patients with anemia.

2.1. Patients

All subjects were subjected to; data collection inform of age, sex, marital status, residence, education, occupation, and socioeconomic status. The diagnosis of AIS was done by clinical examination and CT brain. laboratory investigations done (CBC, INR, random blood glucose) on admission. Entire cases were subjected to measuring severity of stroke using NIHSS score at time of admission and 5 days later for short-term outcome and measuring of serum level of both DD and ferritin on admission. Size of infarction on CT was determined by multiplying area of infarction by number of CT slices and slice thickness. Ischemic infarction size >1.5 cm was categorized as large vessel infarction.

2.2. Specimen collection and preparation

2.2.1. D-dimer

We Collected venous blood using standard sampling tubes for clotting tests; employ sterile 0.11 M sodium citrate solution and maintained a precise mixture of 1 + 9 for sodium citrate and blood. Particle-enhanced immune-turbidimetric assay Latex particles of uniform size were coated with monoclonal antibodies to the DD epitope. The antigen/antibody complexes formed by adding specimens comprising DD with a subsequent increase in the test reactants turbidity. The alteration of absorbance with time was mainly reliant on the concentration of DD epitopes in the specimen. The precipitate was detected turbidimetrically.

2.2.2. Serum ferritin

Serum was prepared from a whole blood specimen acquired by acceptable medical approaches. The Ferritin Quantitative Test Kit was reliant on a solid phase ELISA. Quantitative detection of Human Ferritin concentration in human serum.

2.3. Ethical consideration

The study design was approved by IRB committee in faculty of medicine, Mansoura University (code: MS.21.03.1413). Informed verbal consent was obtained from every patient share in the study following confirmation of confidentiality and privacy. The data collected from patients were not to be utilized in different purposes rather than the current work.

2.4. Statistical analysis

Data analysis was conducted by SPSS software, version 25 (SPSS Inc., PASW statistics, Chicago). Qualitative data were defined by utilizing number and percent. Quantitative data were defined by utilizing median for non-normally distributed data and

mean ± SD for normal distribution of data following testing normality by utilizing Kolmogrov–Smirnov test. Significance of the obtained results was judged at the (≤0.05) level. Mann Whitney U and Kruskal Wallis test were utilized to compare between 2 studied groups and more than 2 studied groups, correspondingly for non-normally distributed data. The Spearman's rank-order correlation is used to determine the strength and direction of a linear correlation between 2 non-normally distributed continuous variables and ordinal variables. Multiple linear regression was utilized assess predictors of continuous normally distributed outcome following log transformation with calculation of R^2.

3. Results

Table 1 shows that mean age of the studied cases is 65.66 years ranging from 35 to 94 years, 54% are females. Regarding complaint, 76% of the studied cases have acute hemiparesis, 20% recurrent hemiparesis, 2% acute onset ataxia and 2% acute homonymous hemianopia. Regarding medical history 76% had hypertension, 30% had cardiac, 14% had history of previous ischemic stroke, 12% had smoking and 6% had other comorbidities.

Table 2 demonstrates that initial NIHSS showing a score ranging from 6 to 15 with the mean is 11.64 while NIHSS at the end of follow-up showing score ranging from 4 to 18 with the mean is 12.16. Regarding CT brain, 64% of the studied cases have large vessel infarction and 36% small vessel infarction. Regarding laboratory finding; median serum ferritin is 78 ranging from 0.13 to 461, median D-dimer is 0.5 ranging from 0.16 to 2.27, mean hemoglobin level is 8.14, mean platelet count is 265.7, mean INR is 1.024 and mean random blood glucose is 165.8.

Table 3 demonstrates that there is no statistically significant correlation between serum ferritin and complaint and associated medical comorbidities. A statistically significant correlation is detected between serum ferritin and history of similar condition ($P = 0.037$) with higher median serum ferritin among cases with no history of similar conditions than cases with positive similar conditions. Regarding relation between D-dimer and complaint, hypertensive cases have statistically significant higher median D-dimer than non-hypertensive cases (0.51 ranging from 0.27 to 0.60 versus 0.51 ranging from 0.16 to 2.27).

Table 4 illustrates statistically significant positive correlation between NIHSS initial and serum ferritin and also between NIHSS at follow-up with serum ferritin (r = 0.236, 0.307, respectively), there was no statistically significant correlation between serum ferritin and the following; hemoglobin level, platelet count, INR and random blood glucose level

Table 1. Socio-demographic characteristics, Complaint, medical history of the studied cases.

	$N = 100$ (%)
Age/years	
Mean ± SD (MIN–MAX)	65.66 ± 11.67(35.0–94.0)
Sex	
Male	46 (46.0)
Female	54 (54.0)
Residence	
Urban	64 (64.0)
Rural	36 (36.0)
Complaint	
Recurrent hemiparesis	20 (20.0)
Acute hemiparesis	76 (76.0)
Acute onset ataxia	2 (2.0)
Acute onset homonymous hemianopia	2 (2.0)
Medical History	
Diabetes	52 (52.0)
Hypertension	76 (76.0)
Cardiac (including atrial fibrillation and ischemic heart disease)	30 (30.0)
Smoking	12 (12.0)
Other comorbidities#	6 (6.0)
History of previous ischemic stroke	14 (14.0)

Table 2. Initial and follow-up NIHSS and Laboratory findings among studied cases.

	Mean ± SD (min–max)
NIHSS initial	11.64 ± 3.44 (6–15)
NIHSS follow-up	12.16 ± 4.33 (4–18)
CT brain	
Small vessel infarction	36 (36%)
Large vessel infarction	64 (64%)
Laboratory findings	
Serum ferritin (Normal value = 12 to 300 ng/mL for males and 12 to 150 ng/mL for females)	
Median (min–max)	78(0.13–461)
Normal	66(66.0%)
Elevated	34(%)
D-dimer (Normal value ≤ 0.5)	
Median (min–max)	0.5 (0.16–2.27)
Normal	52 (52.0%)
Elevated	48 (48%)
Hb(gm/dl) (Normal value is 13.5 to 17.5 gm/dl for men and 12.0 to 15.5 gm/dl for women)	
Mean ± SD	8.14 ± 2.31
Anemic	100 (100%)
Platelets count (Normal value is 150,000–450,000 mcL)	
Mean ± SD	265.7 ± 79.95
Normal	94 (94.0%)
Abnormal	6 (6.0%)
INR (Normal value ≤ 1.1)	
Mean ± SD	1.024 ± 0.06
Random blood glucose (Normal value < 200 mg/dL)	
Mean ± SD	165.8 ± 60.12
Normal	64 (64.0%)
Elevated	36 (36%)

Table 3. Relation between D-dimer and ferritin with complaint and history of the studied cases.

	Ferritin Median (min–max)	Test of significance	D-dimer Median (min–max)	Test of significance
Complaint				
Recurrent hemiparesis	57.5 (0.13–381)	KW = 4.31	0.5 (0.16–0.6)	KW = 7.31
Acute hemiparesis	80 (2.5–461)	$P = 0.230$	0.51 (0.27–2.27)	$P = 0.063$
Acute onset ataxia	102 (96–108)		0.5 (0.5–0.5)	
Acute onset homonymous hemianopia	90 (85–95)		0.53 (0.53–0.53)	
Diabetes				
Non -DM	92.1 (31–382)	z = 1.22	0.50 (0.17–2.27)	z = 0.437
Diabetic	73.45 (0.13–461)	$P = 0.269$	0.505(0.16–0.7)	$P = 0.508$
Hypertension				
Non hypertensive	89.5 (50–461)	z = 0.468	0.5 (0.27–0.60)	z = 2.24
Hypertensive	77.5 (0.13–411)	$P = 0.640$	0.51 (0.16–2.27)	$P = 0.025$[a]
Cardiac disease				
Non cardiac	77 (2.5–411)	z = 1.85	0.5 (0.16–0.70)	z = 1.04
cardiac	109 (0.13–461)	$P = 0.064$	0.51 (0.4–2.27)	$P = 0.297$
Smoking				
Non smoker	78 (0.13–461)	z = 0.297	0.5 (0.16–2.27)	z = 0.995
Smoker	83 (31–365)	$P = 0.766$	0.505 (0.17–0.52)	$P = 0.320$
History previous ischemic stroke				
No	90 (0.13–461)	z = 2.09	0.51 (0.16–2.27)	z = 1.64
Yes	55 (31–381)	$P = 0.037$[a]	0.5 (0.17–0.60)	$P = 0.101$

KW, Kruskal Wallis test; z, Mann Whitney U test.
[a] Statistically significant.

Table 4. Correlation between D-dimer and ferritin and NIHSS initial and at short-term follow-up and between ferritin and laboratory findings among the studied cases.

	Ferritin	D-dimer
NIHSS		
NIHSS initial	r = 0.236 $P = 0.018$*	r = 0.956 $P = 0.001$*
NIHSS follow-up	r = 0.0.307 $P = 0.002$*	r = 0.868 $P = 0.001$*
Laboratory Findings		
Hb(gm/dl)	r = 0.123 $P = 0.223$	r = −0.191 $P = 0.057$
Platelets count	r = 0.095 $P = 0.349$	r = 0.114 $P = 0.257$
INR	r = −0.154 $P = 0.125$	r = −0.017 $P = 0.864$
Random blood glucose	r = 0.032 $P = 0.754$	r = −0.109 $P = 0.279$

($P > 0.05$). There was statistically significant positive correlation between D-dimer and NIHSS initial (r = 0.956, $P = 0.001$) and between D-dimer & NIHSS at last short-term follow-up (r = 0.868, $P = 0.001$). There was a non-statistically significant correlation between D-Dimer and laboratory findings among studied cases($P > 0.05$).

Table 5 shows that there was a non-statistically significant relation between serum ferritin level and administration of thrombolytic therapy. There was statistically significant relation between serum ferritin level and CT brain results as regard small and large vessel infarction with higher median ferritin is detected among cases with large vessel than small vessel disease. There was no significant relation between D-Dimer and liver function test among studied cases. Median D-dimer was higher among cases administered thrombolytic therapy with statistically significant association between them ($P = 0.006$). There was statistically significant relation between D-dimer level and CT brain results ($P < 0.05$) with higher d-dimer among cases with large vessel than small vessel diseases.

Table 6 illustrates that increase D-dimer and serum ferritin are statistically significant predictors of NIHSS at last short-term follow-up with 52.1% of NIHSS at last follow-up is determined by changes in

Table 5. Relation between D-Dimer and ferritin and liver function test, thrombolytic therapy administration and Ct bran findings among the studied cases.

	Ferritin Median (min–max)	Test of significance	D-dimer Median (min–max)	Test of significance
Thrombolytic administration				
No	85.5(0.13–383)	z = 0.132	0.5(0.16–2.27)	z = 2.74
Yes	75(38–461)	$P = 0.895$	0.56(0.50–0.6)	$P = 0.006$*
CT brain				
Small vessel infarction	74.45(31–461)	z = 1.961	0.4(0.17–0.60)	z = 1.981
Large vessel infarction	85.5(0.13–411)	$P = 0.05$*	0.64(0.16–2.27)	$P = 0.04$*

Z:Mann Whitney U test.

Table 6. Multiple linear regression of predictors of NIHSS among studied cases.

	Standardized Coefficients	T	*P* value	95% Confidence Interval for B	
	Beta			Lower Bound	Upper Bound
(Constant)	7.46	8.588	0.000	5.738	9.188
Serum ferritin	0.229	2.589	0.011	0.002	0.014
D-dimer	0.425	4.812	0.000	3.965	9.533
R Square = 0.521					

D-Dimer & serum ferritin with the following prediction equation (NIHSS = 7.46 + 0.425*D-dimer+0.229* serum ferritin) (Table 7). illustrates that increase initial NIHSS is a statistically significant predictors of serum ferritin with 18.9% serum ferritin is determined by changes in NHSS the following prediction equation (serum ferritin = 208.85 + 0.256* NIHSS initial) (Table 8). demonstrates that increase presence of cardiac disease, thrombolytic therapy administration, NIHSS initial are statistically significant predictors of D-dimer among studied cases with 54.5% of D-dimer is predicted by changes in previous factors with the following prediction equation (D-dimer = 0.346 + 0.273* cardiac −0.200* thrombolytic+0.481* NIHSS initial).

4. Discussion

AIS has been considered as primary cause of death globally. Currently, intervention could significantly enhance outcomes with a subsequent reduction of disability. AIS has been demonstrated to be associated with a great financial burden, since 1/3 of surviving stroke cases remain dependent in daily activities (Helmy et al., 2021). Studies have been conducted to determine the factors that play an essential role with regard to the formulation of AIS prognosis. Prognostic markers, that have gained major interest recently, are serum ferritin and D-dimer (Siegbahn et al., 2016).

Thus, the aim of the current study was to evaluate the correlation between serum levels of both ferritin and D-dimer and severity of AIS at time of presentation and its relationship with the short-term outcome of patients. The present study was an observational prospective study with analytic component that was carried out on 100 patients attending neurology department at Mansoura university, the mean age of the studied cases was 65.66 years ranging from 35 to 94 years, 54% were females, 52% not working, 64% from urban areas, 80% married, presenting with acute ischemic stroke. Of note, there were limited numbers of studies that discussed the role of ferritin in the context of stroke. Most of previous researches were mostly emphasized on D-dimer alone.

The present study displayed that of 48% and 34% the studied cases were associated with significant increases in both D-dimer and ferritin respectively. This came in the same line with several studies which have demonstrated that; D-dimer values were significantly greater among cases with AIS in comparison with normal control group (Helmy

Table 7. Multiple linear regression of predictors of serum ferritin among studied cases.

Model	B	t	*P* value	95% Confidence Interval for β	
				Lower Bound	Upper Bound
(Constant)	208.847	0.578	0.565	−509.983	927.677
Age	−0.051	−0.390	0.697	−3.334	2.240
Sex	0.074	0.438	0.663	−65.877	103.036
DM	0.044	0.243	0.809	−79.061	101.077
HTN	−0.043	−0.371	0.712	−80.478	55.192
Cardiac	0.170	1.531	0.130	−13.958	107.232
Smoking	−0.123	−0.838	0.404	−159.693	64.980
other comorbidities	0.115	0.981	0.330	−62.426	183.867
history of similar condition	−0.086	−0.781	0.437	−110.708	48.285
Thrombolytic therapy administration	−0.085	−0.685	0.495	−113.514	55.373
Consanguinity	0.016	0.144	0.886	−86.085	99.526
NIHSS initial	0.256	2.094	0.039*	0.472	18.313
HB	0.171	1.368	0.175	−4.239	22.905
WBC	0.086	0.567	0.572	−20.117	36.170
PLT	0.056	0.470	0.639	−0.286	0.464
INR	−0.159	−1.435	0.155	−770.281	124.603
RBG	−0.132	−0.737	0.463	−1.027	0.471
R Square = 0.189					

Table 8. Multiple linear regression of predictors of D-dimer among studied cases.

	β	T	*p* value	95% Confidence Interval for β	
				Lower bound	Upper bound
(Constant)	0.346	0.590	0.556	−0.819	1.511
Age	−0.160	−1.642	0.104	−0.008	0.001
Sex	0.076	0.601	0.550	−0.096	0.178
DM	−0.099	−0.733	0.466	−0.200	0.092
HTN	0.103	1.187	0.239	−0.044	0.176
Cardiac	0.273	3.280	0.002*	0.064	0.260
Smoking	−0.090	−0.825	0.412	−0.258	0.107
other comorbidities	0.016	0.187	0.852	−0.181	0.218
history of similar condition	0.032	0.392	0.696	−0.103	0.154
Thrombolytic therapy administration	−0.200	−2.157	0.034*	−0.285	−0.012
NIHSS initial	0.456	4.975	0.001*	0.022	0.051
HB	−0.145	−1.547	0.126	−0.039	0.005
WBC	−0.116	−1.022	0.310	−0.069	0.022
PLT	0.064	0.717	0.476	0.000	0.001
INR	0.051	0.618	0.538	−0.500	0.951
RBG	0.027	0.197	0.844	−0.001	0.001
R2 = 0.545					

et al., 2021; Siegbahn et al., 2016; Zi and Shuai, 2014; Garg et al., 2020).

With regard stroke scale, the current study revealed that; there was a statistically significant positive relationship between D-dimer and NIHSS initial and between D-dimer & NIHSS at short-term follow-up. It demonstrated that presence of cardiac disease, thrombolytic therapy administration, NIHSS initial are statistically significant predictors of D-dimer among the studied cases with 54.5% of D-dimer is predicted by changes in previous factors.

D-dimer is a final soluble fibrin degradation product that undergoes plasmin-mediated degradation (Abbas et al., 2021). There are a lot of potential explanations for why plasma DD values could be related to poor outcomes in the context if cases with AIS. For examples, plasma DD value increases in the context of blood coagulation and fibrin degradation and may be an indicator of thrombosis according to the primary mechanisms (Yuan et al., 2021; Weitz et al., 2017).

Similarly, **Abbas and colleagues** (Zi and Shuai, 2014) have found that; there was a significant relationship between DD at admission and D-dimer after 24 h and NIHSS. Also, **Ramos-Pachón and colleagues** (Matsuo et al., 2000) have selected (NIHSS≥10) as the best cut off point in prediction of large vessel occlusion (LVO).They have displayed that severe strokes (NIHSS≥10) had greater values of DD in comparison with mild or moderate strokes (NIHSS<10).

In the context of infarction size and DD value, the present study demonstrated that there was a significant relationship between both D-dimer and CT brain results as regard small and large vessel infarction with higher median ferritin is detected among cases with large vessel than small vessel disease.

Likewise, **Zi and Shuai** (Helmy et al., 2021) have demonstrated that; DD values increased with increasing degree of stroke as described by the NIHSS score and infarction size. In accordance, **Ramos-Pachón and colleagues** (Matsuo et al., 2000) have demonstrated that; D-dimer has been considered as an independent predictor of LVO. Specificity (Sp) and positive predictive value to rule out or determine LVO were greater when using combined DD values and NIHSS score evaluation instead of NIHSS only.

In addition, **Abbas and colleagues** (Zi and Shuai, 2014) have recorded that; increased DD value beyond 310 ng/mL could play an essential role with regard to the prediction of infarction size >1.5 cm in diffusion-weighted MRI brain with sensitivity (Sn) and Sp (100 and 83%, correspondingly) and admission DD at 24 h at cutoff concentration 350 ng/mL and D1 at cut off value 370 ng/mL are predictors of complicated course with Sn and Sp (100 and 84.6%, correspondingly).

With regard to the relation of D-dimer to the overall outcomes, the current study demonstrated that; increased DD was accompanied by poor short-term outcome for acute ischemic stroke, proposing the possible role of plasma DD value as a predictive marker in the context of poor outcomes among cases with AIS.

This can be explained that a high plasma DD values could be associated with resistance to the

endogenous fibrinolytic system and interfere with TE development (Kogan et al., 2016; Ramos-Pachó et al., 2021). In addition, plasma DD triggers the immune system with a subsequent alterations in inflammatory mediators values which include IL-1, TNF-alpha, IL-6, and IL-8 (Rallidis et al., 2008). Stimulated inflammation could participate in the pathologic change in cases with AIS (Urbach et al., 2002).

Similarly, **Yao and colleagues** (Shorr et al., 2002) have demonstrated that; Higher plasma DD value on admission was accompanied by poor outcomes. The best differentiating factor for poor outcomes was a plasma DD value $\geq$ 0.315 mg/L. A Swiss study by **Hsu and colleagues** (Castellanos et al., 2002) have recorded that a high plasma DD values denotes adverse outcomes in cases with AIS receiving intravenous thrombolysis.

In addition, **Yuan and colleagues** (Garg et al., 2020) have revealed that the high DD values on admission were correlated with increased possibility of all-cause mortality, 5-day relapse, and poor outcomes in the context of cases with AIS or TIA. Also, **Hsu and colleagues** have demonstrated that; patients with adverse outcomes had significantly higher values of DD than those with promising outcomes. Following adjustment for clinical variables, a higher value of DD remained significantly accompanied by adverse outcomes (Castellanos et al., 2002).

Higher serum ferritin values denote greater body stores of iron. In addition, this is reflected on the iron stores in the cerebral tissue. Once cerebral ischaemia happens throughout CVA, additional iron will be released from the affected cells owing to their greater iron stores (Ramos-Pachó et al., 2021).

In the context of stroke severity and serum ferritin, the current study displayed that increased serum ferritin was statistically significant predictor of increase in NIHSS at short-term follow-up with 52.1% of NIHSS at last follow-up is determined by changes in D-Dimer & serum ferritin with the following prediction equation (NIHSS = 7.46 + 0.425*D-dimer+0.229* serum ferritin).

This came in the same line with **Garg and colleagues** (Siegbahn et al., 2016) who have displayed that; there was a statistically significant negative correlation between serum ferritin levels and Canadian stroke scale (CSS) scores at admission as well as on the 6th day in the study population. The average serum ferritin in the group with 'more severe stroke' on admission (CSS $\leq$7) was significantly higher compared to the group with 'less severe stroke' on admission (CSS >7).

Also, **Erdemoglu and Ozbakir** observed that serum ferritin values were higher in cases with large lesion size (Yao et al., 2019).

In addition, **Koul and colleagues** (Hsu et al., 2016) have displayed that there was a significant association between the values of serum ferritin and NIHSS and modified Rankin scale, both of which are utilized to assess the stroke degree. As a result, it is recommended that the admission-day serum ferritin correlates with the stroke degree on admission.

In a comparable research conducted on sixty cases with AIS, serum ferritin was measured at admission, and the stroke degree was evaluated by the NIHSS. Of them, thirty five had high serum ferritin and twenty five had normal serum ferritin at admission. Of these thirty five cases with high serum ferritin, twenty two had severe stroke (based on NIHSS) and thirteen had moderate stroke. Of twenty five cases with low serum ferritin at admission, none had severe stroke. As a result, the study concluded that there was a positive association between serum ferritin and NIHSS scores (Erdemoglu and Ozbakir, 2002).

With regard to the relation of ferritin to short-term outcomes, the current study demonstrated that; elevated serum ferritin was associated with poor outcomes compared to cases with normal ferritin. It illustrated statistically significant positive relationship between NIHSS initial and serum ferritin and also between NIHSS at follow-up with serum ferritin.

Similarly, **Garg and colleagues** (Siegbahn et al., 2016) have displayed that; of the fifty subjects recruited, 22 deteriorated. The average serum ferritin on admission in deteriorated cases was significantly greater than in cases who didn't deteriorate. The average serum ferritin level on the 6th day was significantly greater in deteriorated cases in comparison with those who didn't deteriorate.

In agreement, **Pankaj and colleagues** (Koul et al., 2017) conducted their study on cases with AIS, and have recorded that the level of serum ferritin has direct relationship with worse prognosis in cases of AIS. The average value of serum ferritin in the improved group (87) was much lesser in comparison with the group clinically deteriorated or died (458.7) among cases of AIS with a statistically significant difference. Likewise in hemorrhagic stroke it was 96.4 in improved group in comparison with 463.9 in deteriorated with a statistically significant difference.

In the context of infarction size and serum ferritin level, the present study demonstrated that there was a statistically significant relation between serum ferritin level and CT brain results as regard small and large vessel infarction with higher median ferritin is detected among cases with large vessel than small vessel disease.

Likewise, **Erdemoglu and Ozbakir** (Yao et al., 2019) have demonstrated in the context of AIS that,

the serum ferritin values were significantly greater in cases with large lesion size and worsened neurological condition throughout follow-up.

In addition, **Demerdash and colleagues** (Egovindarajulu et al., 2016) noticed significantly higher values of serum ferritin in cases with larger-sized lesions and worsened neurological state throughout follow-up. Cerebrospinal fluid and serum ferritin values were correlated with neurological deficits. They revealed that increased levels of cerebrospinal fluid and serum ferritin correlate with the stroke severity and could denote a poor prognosis with regard to neurological deterioration in the context of AIS cases.

4.1. Limitations

Despite the promising outcomes of the current study being a single-center study has been considered the main limitation. Also, small sample size is another limitation. Also, further comparison between hemorrhagic and ischemic stroke is warranted and investigating the role of hemorrhagic transformation in AIS.

4.2. Conclusion

In the context of AIS, several blood biomarkers can be used to assess severity and short-term outcome. Elevated plasma DD levels and serum ferritin were significantly accompanied by poor short-term outcomes, determined by NIHSS follow-up, recommending the potential role of plasma DD and serum ferritin levels as predictive markers for short-term poor outcome in cases with AIS. Both serum ferritin and DD levels were significantly associated with large vessel infarction determined by CT.

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Conflicts of interest

No conflict of interest.

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