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Original Article

The Prognostic Value of Serum D-Dimer in Acute Ischemic Stroke Patients Prospective Cohort Study

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Abstract *- Acute ischemic stroke (AIS) is considered one of the major causes of death and long-term functional disability. This study aims to evaluate the predictive role of serum D-dimer upon admission. Results: This prospective cohort study included (n=191) patients with AIS admitted to the hospital within 48 hours from the onset of symptoms. Serum D-dimer levels were measured upon admission, stroke severity was determined by (NIHSS), and functional outcomes were assessed on the modified Rankin scale (mRs) after 30 days. Higher levels of serum D-dimer were associated with more severe strokes (OR = 1.5, 95% CI = 1.1–2.4). High serum D-dimer levels were an independent risk factor for predicting a bad prognosis (OR = 19.3, 95% CI = 5.9–62.7). The cut-off point for a bad prognosis was D-dimer =0.79 mg/L with a sensitivity of 92.6% and 88% specificity. The mortality rate among patients was about 8.4% (16 patients) after a 30-day follow-up. Patients who died recorded higher values of serum D-dimer. Conclusion: Elevated serum D-dimer levels on admission in patients with AIS were associated with higher stroke severity, bad prognosis, and high mortality rate at 30 days.*

Keywords *- Acute ischemic stroke, D-dimer, Prognosis.*

1. Introduction

Stroke is a major public health problem and carries enormous economic and social burdens. Data are still limited to the epidemiology of stroke besides mortality statistics. Stroke is divided into two main categories: ischemic stroke and hemorrhagic stroke. Ischemic stroke is caused by an interruption of blood flow to a part of the brain resulting in sudden functional disability, while a rupture of a blood vessel or an abnormal vascular structure [1] causes a hemorrhagic stroke.

Many factors have been studied recently to determine the prognosis of AIS. However, it is still difficult to predict outcomes by clinical practitioners, so it has been useful to find new predictors, including serum D-dimer, to aid in managing AIS. The D-dimer serum is relatively stable, resistant to ex vivo activation and has a long half-life [2].

2. Patients and Methods

It is a prospective cohort, observational, analytical, and prognostic study. The study included AIS patients between 18 and 80 admitted to the hospital within 48 hours of symptom onset. Patients who were excluded had one of these conditions: had received oral or intravenous antithrombotic therapy, status epilepticus, cerebral hemorrhage, coma, surgery, trauma, heat disorders, acute and chronic inflammatory diseases, malignancy, pregnancy, deep vein thrombosis (DVT), Pulmonary Embolism (PE), and previous functional impairment of any cause (mRs>2).

The patient's clinical history was documented, including age, gender and the presence of risk factors such as smoking, alcohol consumption, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, and a history of ischemic stroke. A comprehensive neurological examination and assessment of stroke severity based on the NIHSS score were performed. Serum D-dimer (mg/L) levels were measured within 48 hours of symptom onset. The basic serological parameters (CRP, TG, Cholesterol, LDL, PT, and INR) were also calibrated. Cardiac echocardiography, Holter 24-48 hours, and cervical arterial echography were performed for all patients. The prognosis was determined according to the mRs Scale after a month (30 days). Therefore, patients were split into three groups (mRs≤2 = good functional outcome, mRs≥3 = poor functional outcome, mRs=6 death).

2.1. Ethical Consideration

All patients were provided with complete and clear informed consent after the discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

2.2. Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 25. Basic Descriptive statistics included means, standard deviations (SD), Frequency and percentages. Differences among different groups were examined using the chi-square test or Fisher exact test. One way Anova was used was to compare between the groups. The receiver operating characteristics (ROC) curve was constructed, and the area under the curve (AUC) was established to assess the peak platelet's ability to predict an outcome. P- value <0.05 was considered statistically significant.

Table 1. Results of comparing all studied variables in acute ischemic stroke patients according to the two severity groups

Variable		Mild to moderate (132)	Severe (59)	*P value
Age		63.1 ± 11.4	65.2 ± 10	0.238
Female gender		56 (42.2%)	32 (54.2%)	0.130
Smoking		70 (53%)	25 (42.4%)	0.173
Alcohol		7 (5.3%)	2 (3.4%)	0.564
History of hyperlipidemia		9 (6.8%)	5 (8.5%)	0.685
CAD		20 (15.2%)	32 (54.2%)	<0.001**
Diabetes mellitus		43 (32.6%)	33 (55.9%)	0.002
Hypertension		80 (60.6%)	33 (55.9%)	0.544
Atrial fibrillation		4 (3%)	14 (23.7%)	<0.001
History of ischemic stroke		23 (17.4%)	20 (33.9%)	0.012
OCSP	TACS	13 (9.8%)	32 (54.2%)	<0.001
	PACS	33 (25%)	13 (22%)	
	POCS	13 (9.8%)	6 (10.2%)	
	LACS	66 (50%)	2 (3.4%)	
TOAST	LAA	27 (20.5%)	30 (50.8%)	<0.001
	CE	21 (15.9%)	25 (42.4%)	
	SVD	65 (49.2%)	2 (3.4%)	
	Cryptogenic	19 (14.4%)	2 (3.4%)	
CRP		10.8 ± 14.1	17.4 ± 28.4	0.097
TG		188.9 ± 113.7	156.1 ± 69.7	0.012
Total cholesterol		171.6 ± 56.7	166 ± 56.2	0.533
LDL		94.9 ± 90	76.7 ± 33.5	0.139
D-dimer		0.88 ± 0.93	1.79 ± 1.6	<0.001

**p-value is significant at the 0.05 level. **p-value is significant at the 0.01 level (highly significant). NIHSS, National Institutes of Health Stroke Scale; CAD coronary artery disease; OCSP, Oxfordshire Community Stroke Project Subtype; TACS, Total Anterior Circulation Syndrome; PACS, Partial Anterior Circulation Syndrome; POCS, Posterior Circulation Syndrome; LACS, Lacunar Syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; cryptogenic, undetermined cause; CRP, C-reactive protein; TG, Triglyceride; LDL, Low-density lipoproteins.*

Table 2. Results of multivariate analysis to isolate the statistically independent factors for predicting severe injury in acute ischemic stroke patients.

Variable		OR*	95% CI **		P value
			Lower limit	Upper limit	
Diabetes mellitus		1.4	0.6	3.2	0.422
CAD		2.7	1.4	6.4	0.024
Atrial fibrillation		4	1	16.7	0.050
History of ischemic stroke		0.8	0.3	2	0.619
TOAST	LAA compared to SAD	25.9	5.5	122.3	<0.001
	CE compared to SAD	10	1.9	53.3	0.007
D-dimer (per unit)		1.5	1.1	2.4	0.035
TG (per unit)		1	0.9	1	0.058

OD, Odds Ratio; CI, confidence Interval.*

CAD coronary artery disease; ; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; TG, Triglyceride

Table 3. Results of comparing the characteristics of acute ischemic stroke patients by the two prognosis groups:

Variable	Good functional outcome (83)	Poor functional outcome (108)	*P value
Age	60.5 ± 11.3	66.3 ± 10.2	<0.001**
Female gender	28 (33.7%)	48 (44.5%)	0.003
Smoking	51 (61.4%)	44 (40.7%)	0.073
Alcohol	5 (6%)	4 (3.7%)	0.453
History of hyperlipidemia	8 (9.6%)	6 (5.6 %)	0.283
CAD	7 (8.4%)	45 (41.7%)	<0.001
Diabetes mellitus	14 (16.9%)	62 (57.4%)	<0.001
Hypertension	47 (56.6%)	66 (61.1%)	0.532
Atrial fibrillation	2 (2.4%)	16 (14.8%)	0.004
History of ischemic stroke	8 (9.6%)	35 (32.4%)	<0.001

OCSP	**TACS**	5 (6%)	40 (37%)	<0.001
	PACS	10 (12%)	36 (33.3%)	
	POCS	5 (6%)	14 (13%)	
	LACS	62 (74.7%)	6 (5.6%)	
TOAST	**LAA**	12 (14.5%)	45 (41.7%)	<0.001
	CE	1 (1.2%)	45 (41.7%)	
	SVD	61 (73.5%)	6 (5.6%)	
	Cryptogenic	9 (10.8%)	12 (11.1%)	
CRP		10 ± 16	15 ± 22	0.078
TG		192.3 ± 113.2	168.4 ± 93.8	0.114
Total cholesterol		171.9 ± 59.1	168.3 ± 54.6	0.666
LDL		92.3 ± 58.2	86.9 ± 88.9	0.647
D-dimer		0.58 ± 0.56	1.60 ± 1.43	<0.001

**p-value is significant at the 0.05 level. **p-value is significant at the 0.01 level (highly significant). NIHSS, National Institutes of Health Stroke Scale; CAD coronary artery disease; OCSP, Oxfordshire Community Stroke Project Subtype; TACS, Total Anterior Circulation Syndrome; PACS, Partial Anterior Circulation Syndrome; POCS, Posterior Circulation Syndrome; LACS, Lacunar Syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; cryptogenic, undetermined cause; CRP, C-reactive protein; TG, Triglyceride; LDL, Low-density lipoproteins.*

Table 4. Results of multivariate analysis to isolate the statistically independent factors for predicting bad prognosis in acute ischemic stroke patients

Variable		OR*	95% CI **		P value
			Lower limit	Upper limit	
Age (for every extra one)		1	0.9	1.1	0.163
Female		1.3	0.6	3.2	0.564
Diabetes mellitus		4.3	1.2	15.5	0.029
CAD		2.1	0.5	9.6	0.367
Atrial fibrillation		7	1.5	31	0.011
History of ischemic stroke		4.7	1.5	14.7	0.009
TOAST	**LAA compared to SAD**	37	6.5	211	<0.001
	CE compared to SAD	50	12	250	<0.001
D-dimer (per unit)		19.3	5.9	62.7	<0.001

**OD, Odds Ratio; ** CI, confidence Interval.*
CAD coronary artery disease; ; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; TG, Triglyceride

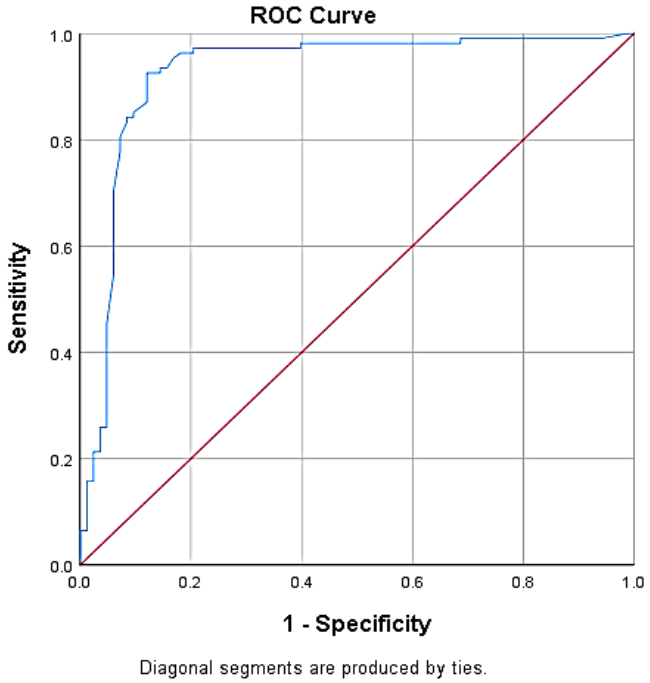

Fig. 1 ROC diagram showing the relationship between D-dimer values and bad prognosis.

Table 5. Comparison of the characteristics of AIS patients by the two D-Dimer groups

Variable		(81)D-dimer ≤ 0.79	(110)D-dimer > 0.79	*P value
Age		61.1 ± 11.6	65.8 ± 10.2	0.003**
Female gender		28 (34.6%)	60 (54.5%)	0.006
Smoking		47 (58%)	48 (43.6%)	0.051
Alcohol		4 (4.9%)	4 (4.5%)	0.899
History of hyperlipidemia		8 (9.9%)	6 (5.5%)	0.247
CAD		6 (7.4%)	46 (41.8%)	<0.001
Diabetes mellitus		18 (22.2%)	58 (52.7%)	<0.001
Hypertension		48 (59.3%)	65 (59.1%)	0.981
Atrial fibrillation		1 (1.2%)	17 (15.5%)	0.001
History of ischemic stroke		9 (11.1%)	34 (30.9%)	0.001
OCSP	TACS	6 (7.4%)	6 (7.4%)	<0.001
	PACS	11 (13.6%)	11 (13.6%)	
	POCS	7 (8.6%)	7 (8.6%)	
	LACS	57 (70.4%)	57 (70.4%)	
TOAST	LAA	13 (16%)	13 (16%)	<0.001
	CE	3 (3.7%)	3 (3.7%)	
	SVD	56 (69.1%)	56 (69.1%)	
	Cryptogenic	9 (11.1%)	9 (11.1%)	
NIHSS		9.7 ± 2.9	15.2 ± 4.4	<0.001
MRs		1 (2)	3 (2)	<0.001
CRP		10.1 ± 15.2	14.9 ± 22.5	0.099
TG		191 ± 113.9	169.9 ± 93.8	0.164
Total cholesterol		170.4 ± 57.8	169.4 ± 55.7	0.909
LDL		92.3 ± 57	87 ± 88.9	0.648

**p-value is significant at the 0.05 level. **p-value is significant at the 0.01 level (highly significant). NIHSS, National Institutes of Health Stroke Scale; CAD coronary artery disease; OCSP, Oxfordshire Community Stroke Project Subtype; TACS, Total Anterior Circulation Syndrome; PACS, Partial Anterior Circulation Syndrome; POCS, Posterior Circulation Syndrome; LACS, Lacunar Syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; cryptogenic, undetermined cause; CRP, C-reactive protein; TG, Triglyceride; LDL, Low-density lipoproteins.*

Table 6. Comparison of characteristics of acute ischemic stroke patients between death and survivor groups.

Variable		Survived (175)	Died (16)	*P value
Age		63.2 ± 11	70.7 ± 9.1	0.008**
Female gender		79 (45.1%)	9 (56.2%)	0.394
Smoking		91 (52%)	4 (25%)	0.054
Alcohol		8 (4.6%)	1 (6.3%)	0.762
History of hyperlipidemia		13 (7.4%)	1 (6.3%)	0.863
CAD		38 (21.7%)	14 (87.5%)	<0.001
Diabetes mellitus		64 (36.6%)	12 (75%)	0.003
Hypertension		100 (57.1%)	13 (81.3%)	0.060
Atrial fibrillation		10 (5.7%)	8 (50%)	<0.001
History of ischemic stroke		36 (20.6%)	7 (43.8%)	0.034
NIHSS		12.2 ± 4.2	19.8 ± 3.5	<0.001
D-dimer		1.06 ± 0.08	2.06 ± 0.52	<0.001
OCSP	TACS	33 (18.9%)	12 (75%)	<0.001
	PACS	45 (25.7%)	1 (6.3%)	
	POCS	18 (10.3%)	1 (6.3%)	
	LACS	68 (38.9%)	0 (0%)	
TOAST	LAA	53 (30.3%)	4 (25%)	<0.001
	CE	34 (19.4%)	12 (75%)	
	SVD	67 (38.6%)	0 (0%)	
	Cryptogenic	21 (12%)	0 (0%)	
CRP		12.4 ± 20	18 ± 18.1	0.277
TG		182.5 ± 102.6	138.5 ± 10.3	0.103
Total cholesterol		171.4 ± 56.5	152.5 ± 55.1	0.199
LDL		89.8 ± 80	83.3 ± 38.9	0.749

**p-value is significant at the 0.05 level. **p-value is significant at the 0.01 level (highly significant).*

NIHSS, National Institutes of Health Stroke Scale; CAD coronary artery disease; OCSP, Oxfordshire Community Stroke Project Subtype; TACS, Total Anterior Circulation Syndrome; PACS, Partial Anterior Circulation Syndrome; POCS, Posterior Circulation Syndrome; LACS, Lacunar Syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardiac embolism; SVD, Small vessel Disease; cryptogenic, undetermined cause; CRP, C-reactive protein; TG, Triglyceride; LDL, Low-density lipoproteins.

3. Results

The study included (n=191) patients diagnosed with acute ischemic stroke who were admitted to the neurology department in the hospital during the years 2020 and 2021. Male patients were 103 (53.9%), and female patients were 88 (46.1%). The age of the patients ranged between 35 and 80 years old. The severity of the stroke was assessed according to the NIHSS score. Patients were divided into two groups (Mild to moderate injury: when NIHSS ≤ 14 and severe injury when NIHSS > 14).

The mild to moderate severity group constituted 69% (132) of the study patients, while severe injury patients made up only 31% (59), Table 1. The most significant proportion of the study patients is those with a bad prognosis (poor functional outcome when mRs ≥ 3), 57% of the study population, Table 3. To determine the cut-off point of the D-dimer for predicting the poor prognosis, we performed a ROC curve and obtained a result that reflects a close correlation between the value of the D-dimer and poor prognosis. The most sensitive and specific standard point was the D-dimer value = 0.79 mg/L, with a sensitivity of 92.6% and a specificity of 88%, Figure 1. When re-divided the patient's sample into two groups according to the new cut-off point to compare all variables according to this value, we obtained the following results in Table 5. In this study, the number of patients who died was 16 (n = 8.4%) Table 6.

4. Discussion

The research sample included 191 patients with an average age of (63.8) years. The males were 53.9% of the patients, which is in line with the fact that the male sex is one of the non-modifiable risk factors in ischemic stroke. Stroke throughout human life is higher in females because the average lifespan of females is higher than the average of males [3], and the risk of stroke, in its two types, "ischemic and hemorrhagic", doubles every decade after the age of 55 [4, 5].

When we studied the relationship of different variables with stroke severity, estimated according to the NIHSS scale, the mild to moderate severity group constituted 69% of the patients, while the proportion of severe severity patients was only 31%. This difference in the distribution may be attributed to the fact that the largest proportion of the study patients was those with the lacunar syndrome and partial anterior circulation syndrome, Table 1. We found by multivariate analysis that high D-dimer values on admission, CAD, Atrial fibrillation, and cause of stroke according to TOAST classification are independent factors for predicting the severity of the stroke, and this is consistent with other studies that have shown that higher levels of serum D-dimer are associated with advanced age, greater severity of AIS according to NIHSS, increased infarct volume, cause of a stroke as classified by TOAST, and poor functional outcomes according to the mRs scale [6,7,8]. When studying the relationship of different variables with prognosis assessed according to the mRs scale after 30 days, it was found that the largest proportion of the study patients is those with bad prognosis (57%), with a higher average age in the bad prognosis group compared to the good prognosis group, and this is consistent with most international studies which demonstrate that age is a risk factor for bad prognosis in stroke patients. Higher values of serum D-dimer were recorded in the bad prognosis group, as it was found that patients with cardiac embolism and LAA according to TOAST classification compared to SVD are the majority of those with bad prognosis with statistical significance ($P < 0.001$), as well as for patients with complete anterior circulation syndrome compared to lacunar syndrome according to the OCSP classification. High D-dimer values had an OR of 19.3 and a 95% confidence interval (5.9–62.7) for predicting poor prognosis, which is consistent with the studies conducted by Yang and colleagues [9], and Kim and colleagues [10], which concluded that high values of serum D-dimer are independently associated with bad prognosis in the acute phase. Our study also agrees with the study conducted by Zhang and colleagues [11], which concluded that high values of D-dimer during the first 24 hours of acute ischemic stroke are independently associated with relapse at day 5 on DWI, death after 30 days and bad prognosis after 30 and 90 days. Our results, however, disagreed with the studies carried out by Squizzato and colleagues [12] and Rallidis and colleagues [13], Which concluded that serum D-dimer levels are not able to predict functional outcomes and attributed the absence of a relationship between them to the fact that the serum D-dimer may be affected by many factors, the most important of which is age. The cut-off point of serum D-dimer that predicts poor functional outcomes is D-dimer 0.79mg/L with a sensitivity of 92.6% and specificity of 88%.

When comparing the mean values of serum D-dimer between stroke cause groups, it was found that these values have higher rates in patients with a cardiac source of emboli, which is in line with numerous studies [14, 15, and 16]. It was explained that the D-dimer might reflect the effectiveness of thrombus formation at the level of the left atrium or the left ventricle. Low values of serum D-dimer were reported in patients with lacunar syndrome and those with SVD compared to the other groups because it produces only very small amounts of D-dimer [17]. Relatively elevated values of serum D-dimer were reported in the unspecified cause group, which is in line with a study by Nezu and colleagues [18], which concluded that AIS patients from the unspecified cause group with elevated serum D-dimer values have a poor long-term prognosis with a higher death rate at discharge. This was attributed to some of these patients being diagnosed with atrial fibrillation or carcinomas [19].

Although the mechanism is unclear, several theories have been proposed to explain the association between serum D-dimer and prognosis in AIS. Serum D-dimer levels rise in cases of thrombosis and fibrinolysis, which makes it reflect a thrombotic state in the body [20, 21]. The high levels of serum D-dimer provide reliable evidence of thromboembolic formation and may reflect the effectiveness of the internal fibrin-resistant system [22, 23] and, finally, the stimulation of serum D-dimer on the immune system, which leads to a change in the levels of inflammatory mediators such as IL-1, TNF-alpha, IL-6, and IL-8 [24, 25]. The resulting inflammatory activation contributes to pathological changes in patients with AIS [26]. The mortality rate among the study patients was about 8.4%, with a total number of 16 upon follow-up for 30 days. The patients who died had Higher values of serum D-dimer were statistically significant ($P < 0.001$), and that is consistent with the study by Zhang and colleagues [11], which concluded that higher values of serum D-dimer are associated with higher rates of death by day 30. The cut-off point of serum D-dimer that predicts death is D-dimer = 1.25 mg/L with a sensitivity of 81.3% and a specificity of 81.1%

5. Conclusion

Elevated serum D-dimer levels on admission in patients with AIS were associated with higher stroke severity, poor prognosis, and high mortality rate. According to the TOAST classification, there is a statistically significant relationship between high levels of serum D-dimer on admission and the cause of stroke. There is a statistically significant relationship between the increase in serum D-dimer levels and some clinical syndromes of stroke according to OCSP classification. This indicates the future role serum D-dimer may play in revealing the underlying cause of idiopathic ischemic stroke.

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