ORIGINAL ARTICLE

Prognostic Value of Serum D-Dimer in Noncardioembolic Ischemic Stroke

Tae-Won Kim MD, In-Uk Song, Sung-Woo Chung

ABSTRACT: ***Background:*** Although D-dimer levels are significantly associated with cardioembolic infarction, the significance of D-dimer levels in relation to the severity and functional outcomes of other stroke subtypes, such as lacunar and large artery atherosclerosis infarction, remains unclear. The purpose of this study was to evaluate whether elevated initial D-dimer levels are significantly and cross-sectionally associated with poor functional outcomes at each time point during a 9-month follow-up period. We also investigated the significance of D-dimer levels in longitudinal temporal changes of functional outcomes in these patients. ***Methods:*** We recruited 146 patients with lacunar infarction and 161 patients with large artery atherosclerosis infarction who were consecutively admitted to our hospital after acute stroke. Serum D-dimer levels were evaluated initially and the modified Rankin scale were measured initially and at 1-, 3-, 6-, and 9-month follow-up visits. ***Results:*** Patients with higher D-dimer levels had significantly worse initial functional outcomes, and these worse outcomes were maintained throughout the 9-month follow-up period compared with the low D-dimer group. However, regardless of stroke subtype, D-dimer levels did not influence long-term changes in functional outcomes over the 9-month follow-up period. ***Conclusion:*** This study suggests that elevated D-dimer levels can be used as a surrogate marker for poor functional outcomes only during the acute stage. Further evaluation of serum D-dimer levels could provide a helpful predictive marker for stroke prognosis.

RÉSUMÉ: Valeur pronostique de la concentration de D-dimères dans le cas d'AVC ischémiques non cardio-emboliques. ***Contexte:*** Bien qu'une concentration élevée de D-dimères (DD) soit associée de façon significative à des infarctus d'origine cardio-embolique, l'importance de ces DD en rapport avec la gravité et les conséquences fonctionnelles d'autres types d'AVC, par exemple les infarctus lacunaires et ceux attribuables à l'athérosclérose d'une artère importante, demeurent floues. L'objectif de cette étude a donc été d'évaluer dans quelle mesure des concentrations élevées de DD étaient initialement associées de façon significative et transversalement à de sévères conséquences fonctionnelles au cours d'une période de suivi de 9 mois. Nous avons aussi exploré l'importance des concentrations de DD en lien avec les changements temporels affectant nos patients et les conséquences fonctionnelles de leur AVC. ***Méthodes:*** Nous avons recruté 146 patients victimes d'un infarctus lacunaire ainsi que 161 autres ayant été victimes d'un infarctus attribuable à l'athérosclérose d'une artère et hospitalisés à la suite d'un AVC aigu. Dans un premier temps, leurs concentrations de DD ont été mesurées. Nous avons ensuite évalué ces mêmes patients une première fois en fonction de l'échelle modifiée de Rankin et lors de leurs visites de suivi (1, 3, 6 et 9 mois). ***Résultats:*** Les patients dont la concentration de DD était plus élevée ont initialement montré de sévères conséquences fonctionnelles. Ces conséquences plus sévères n'ont pas varié tout au long de la période de suivi de 9 mois si on les compare à celles du groupe dont la concentration de DD était faible. À long terme toutefois, la concentration de DD n'a pas eu d'impact sur les changements aux conséquences fonctionnelles au cours de la période de suivi de 9 mois, et ce, quels que soient les sous-types d'AVC. ***Conclusions:*** En somme, cette étude suggère qu'une concentration élevée de DD ne peut être utilisée comme marqueur de substitution prédictif de sévères conséquences fonctionnelles que durant la phase aiguë d'un épisode. Cela dit, une étude plus approfondie de la concentration de DD pourrait aboutir à l'apparition d'un marqueur prédictif utile dans les cas de pronostics post-AVC.

Keywords: D-dimer, Functional Outcome, Modified Rankin Scale, Prognosis

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D-dimer is a byproduct of fibrin degradation and reflects thrombin and fibrin turnover.[1] Clinically, serum D-dimer levels are useful for diagnosing venous thromboembolism and thrombotic adverse events in patients with cancer.[2,3]

D-dimer levels have shown consistently significant associations in ischemic stroke, cardioembolic infarction, and stroke related to atrial fibrillation (AF). D-dimer levels are increased in patients with AF, and these high levels are associated with left atrial appendage thrombus.[4,5] Moreover, serum D-dimer levels were reduced by both anticoagulation and cardioversion to sinus rhythm in patients with AF.[5,6]

However, the associations between D-dimer levels and adverse cerebrovascular events have been inconsistent when other stroke subtypes in addition to cardioembolic infarction were evaluated. D-dimer was significantly associated with increased frequencies of stroke, stroke progression, and even death, regardless of stroke subtype in several studies.[7-10] However, one study showed that after excluding venous thrombosis in all stroke patients using imaging studies along with adjustment for confounding factors, neither stroke severity nor total anterior circulation infarction was

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associated with D-dimer levels, and only old age was significantly associated with D-dimer levels.[11]

Because of these equivocal relationships of other stroke subtypes with D-dimer levels, in contrast to the robust significant association of D-dimer with cardioembolism, we evaluated the association between D-dimer levels and long-term functional outcomes in patients with acute lacunar and large artery atherosclerosis (LAA) infarctions.

We first assessed whether elevated initial D-dimer levels were significantly and cross-sectionally associated with poor functional outcomes at each time point during a nine-month follow-up period in non-cardioembolic stroke patients (group effect). Secondly, we examined whether D-dimer levels had a significant impact on longitudinal temporal changes in functional outcomes in these patients (time x group effect).

Methods

Subjects

We performed a retrospective study using the registry of all stroke patients admitted to the Incheon St. Mary Hospital, which was prospectively collected.

Candidate patients were identified by reviewing the registry between September 2012 and August 2014. All patients were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) stroke classification criteria,[12,13] and only patients consecutively admitted to our hospital with lacunar infarction and large artery atherosclerosis (LAA) were included and analyzed. We adopted the modified definition of lacunar infarction as having a pathologic lesion smaller than 20 mm on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) because these infarctions are usually larger on DWI than on computed tomography or conventional brain MRI scans, based on TOAST classification.[14] LAA was diagnosed in patients with brain imaging findings of either significant stenosis (>50%) or occlusion of a major brain artery or cortical branch artery, presumably resulting from atherosclerosis, along with relevant clinical symptoms and DWI lesions (Figure 1).

We enrolled patients within 2 days of onset of an ischemic stroke who had new, corresponding lesions on DWI MRI as well as consistent clinical history and neurological examination. Because of the effect of anticoagulation on serum D-dimer levels, patients could not have taken anticoagulation drugs in the past 3 months, and we required normal activated partial thromboplastin time and prothrombin time international normalized ratio.

Patients were excluded if they had (1) cardioembolic sources such as AF, valvular heart disease, thrombus in the left atrium or ventricle, dilated cardiomyopathy based on echocardiography or 24-hour Holter monitoring; (2) other determined causes or unknown causes on TOAST classification; (3) any laboratory or clinical findings suggestive of infectious, inflammatory, vasculitic, demyelinating, or connective tissue diseases; (4) pre-existing significant disability (defined as modified Rankin scale [mRS] ≥2) from any condition; or (5) a history of stroke in the past 3 months.

Clinical information obtained included age, sex, history of hypertension, diabetes mellitus, dyslipidemia, previous ischemic or hemorrhagic stroke, and current cigarette smoking. All patients underwent a detailed clinical evaluation, including a neurological examination, laboratory tests, chest radiography, 12-lead electrocardiography, 24-hour Holter monitoring, echocardiography, brain MRI, and contrast-enhanced MR angiography, or computed tomography angiography.

The blood sample for serum D-dimer level was obtained immediately after admission to the emergency department, before any intravenous fluids or medications were administered. Serum D-dimer levels were dichotomized into low versus high D-dimer levels using a cutoff of 0.5 mcg/ml.

Assessment of Stroke Severity

Stroke severity was assessed at the time of admission using the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits).[15] We assessed functional stroke outcomes at 1-, 3-, 6-, and 9-month follow-up visits. Clinical assessments of functional outcomes were performed at each time point using the mRS (scores range from 0 [no symptoms] to 6 [death]).[16]

Statistical Analyses

All statistical analyses were performed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL) software.

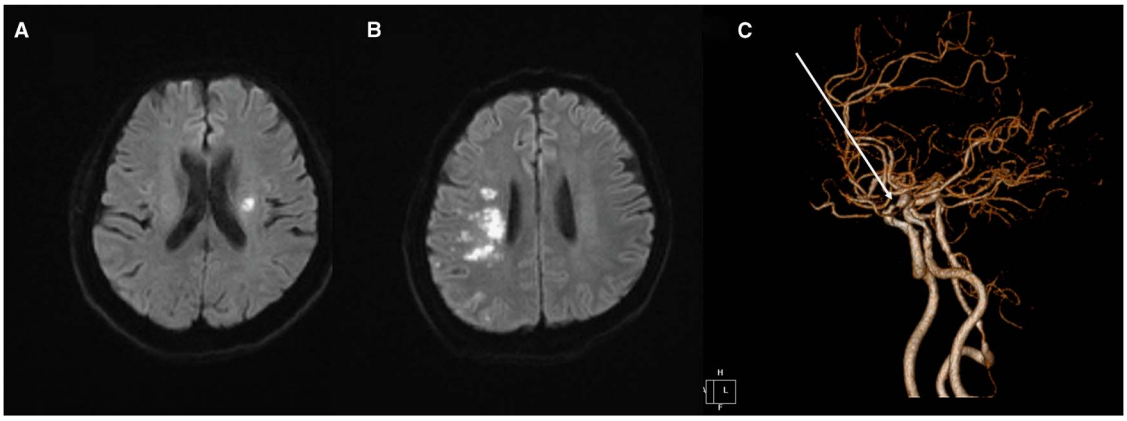

Figure 1: *Representative brain images of lacunar infarction (A) and large artery atherosclerosis (LAA) (B, C). Lacunar infarction was defined as having a pathologic lesion less than 20 mm on diffusion-weighted imaging (DWI) magnetic resonance imaging scans (A) and LAA was diagnosed as having DWI lesions (B) with either significant stenosis (>50%) or occlusion of a relevant major or cortical branch artery (C, white arrow), presumably resulting from atherosclerosis.*

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Independent *t* tests were used to compare continuous variables, and Pearson's chi-squared tests were used to compare categorical variables. Values are expressed as a mean ± standard deviation. Statistical significance was assumed at a false detection rate of less than 5% (i.e. $p < 0.05$). To assess the longitudinal changes in functional outcome based on low versus high D-dimer levels, repeated measures analysis of variance was performed at each time point for all enrolled patients with lacunar and LAA infarctions. Post hoc analysis was further performed to assess changes in functional outcomes from 1 to 3 months and 3 through 6 to 9 months. Variables were entered into our models as covariates when significance levels in univariate analysis fell below $p < 0.20$.

Results

Baseline Characteristics and mRS Scores During the Follow-up Period

Table 1 shows the clinical and demographic characteristics of the lacunar and LAA infarction groups. The two groups differed significantly in age (66.3 ± 10.8 vs 69.4 ± 10.7 years, $p = 0.013$), medical history of hypertension (39% vs 26.7%, $p = 0.021$), the number of deaths during the follow-up period (0.7% vs 8.1%, $p = 0.020$) and mRS scores throughout the entire 9-month follow-up period. The mRS scores of each D-dimer subgroup are described for all enrolled patients and those with lacunar or LAA infarction in Table 2.

When all enrolled patients were classified into high and low D-dimer groups, the high D-dimer group had higher initial NIHSS scores than the low D-dimer group (7.0 ± 6.9 vs 4.5 ± 4.5, $p = 0.005$).

Table 2 shows the effects for group (high vs low D-dimer levels: the inter-group effect), time (from 1 month to 9 months: the intra-group effect), and the group × time interactions (reflecting whether there was a significant influence of serum D-dimer levels on longitudinal changes in mRS scores) adjusted by age and medical history of hypertension. Post hoc analysis in Table 2 shows only group × time interactions of 1 to 3 months and 3, 6, and 9 months.

Analysis of All Enrolled (Noncardioembolic) Patients

There was a significant group effect of D-dimer ($p = 0.008$): the high D-dimer group had significantly higher mRS scores and more deaths than the low D-dimer group for the entire follow-up period (Table 2, Figure 2A). By post hoc analysis of the group effect, the high mRS scores in the high D-dimer group were maintained at both 1and 3 months ($p = 0.003$) and 3, 6, and 9 months ($p = 0.002$).

There was also a significant effect of time ($p < 0.001$), indicating that mRS scores changed significantly during follow-up. This time effect was also maintained for 1 and 3 months ($p = 0.003$) and for 3, 6, and 9 months ($p = 0.002$) in post hoc analysis.

However, significant group × time interactions were not observed for the entire follow-up period ($p = 0.238$, Figure 2A) or for the two periods of post hoc analysis ($p = 0.257$ for 1 and 3 months and $p = 0.207$ for 3, 6, and 9 months), suggesting that there was no impact of serum D-dimer levels on longitudinal changes in mRS scores.

Analysis of Patients With Lacunar Infarction

Although mRS scores were higher in the high D-dimer group than in the low D-dimer group in patients with lacunar infarction throughout the entire follow-up period, this was not

Table 1: Demographic and clinical characteristics between patients with lacunar infarction and those with LAA infarction

	Lacunar infarction (n = 146)	LAA infarction (n = 161)	p value
Age (years)	66.3 ± 10.8	69.4 ± 10.7	0.013*
Sex (female)	67 (45.9)	72 (44.7)	0.837
History of hypertension (%)	57 (39)	43 (26.7)	0.021*
History of diabetes mellitus	98 (67.1)	104 (64.6)	0.641
History of dyslipidemia	107 (73.8)	122 (75.8)	0.690
History of clinical stroke	110 (75.3)	120 (74.5)	0.870
Current smoker	94 (66.2%)	102 (67.1%)	0.869
Initial serum D-dimer levels (mg/l)	0.7 ± 1.4	1.3 ± 2.9	0.039*
Initial serum homocysteine levels (μmol/l)	15.6 ± 7.3	16.4 ± 6.6	0.390
Initial NIHSS	3.9 ± 3.4	7.1 ± 6.9	<0.001**
mRS			
At 1 month	2.5 ± 1.3	3.0 ± 1.5	0.002**
At 3 months	2.1 ± 1.3	2.6 ± 1.6	0.004**
At 6 months	1.9 ± 1.3	2.5 ± 1.7	0.002**
At 9 months	1.9 ± 1.4	2.5 ± 1.8	0.001**
Deaths during the 9 months (%)	1 (0.7%)	13 (8.1%)	0.020*

Values are mean ± standard deviation and the number of patients (%).
*p <0.05, **p <0.01.

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Table 2: Repeated measures ANOVA of mRS in high vs low serum D-dimer levels group analyzed by each stroke etiology including lacunar infarction, LAA infarction, and all enrolled patients

	mRS				Deaths during the 9 months					Post hoc analyses	
	1 month	3 month	6 month	9 month	The number of patients (%)	p value	G effect, p value	T effect, p value	G × T interaction, p value	G × T interaction: 1 to 3 month, p value	G × T interaction: 3 to 9 month, p value
All patients											
Low D-dimer group	2.5 ± 1.3	2.1 ± 1.3	1.9 ± 1.3	1.9 ± 1.4	5 (2.4%)	0.043*	0.008**	<0.001**	0.238	0.256	0.207
High D-dimer group	3.2 ± 1.4	2.9 ± 1.5	2.8 ± 1.5	2.9 ± 1.6	9 (9.0%)						
Lacunar infarction											
Low D-dimer group	2.3 ± 1.2	2.0 ± 1.2	1.8 ± 1.2	1.7 ± 1.2	1 (0.9%)	1.000	0.133	0.114	0.529	0.463	0.559
High D-dimer group	3.0 ± 1.3	2.7 ± 1.2	2.6 ± 1.3	2.6 ± 1.3	0 (0%)						
LAA infarction											
Low D-dimer group	2.6 ± 1.4	2.2 ± 1.4	2.0 ± 1.5	2.0 ± 1.6	4 (4.3%)	0.097	0.085	<0.001**	0.535	0.336	0.463
High D-dimer group	3.3 ± 1.4	3.0 ± 1.6	2.9 ± 1.7	3.0 ± 1.8	9 (13.0%)						

Values are presented as mean ± standard deviation.
ANOVA = analysis of variance; G = group; T = time.
*p <0.05, **p <0.01.

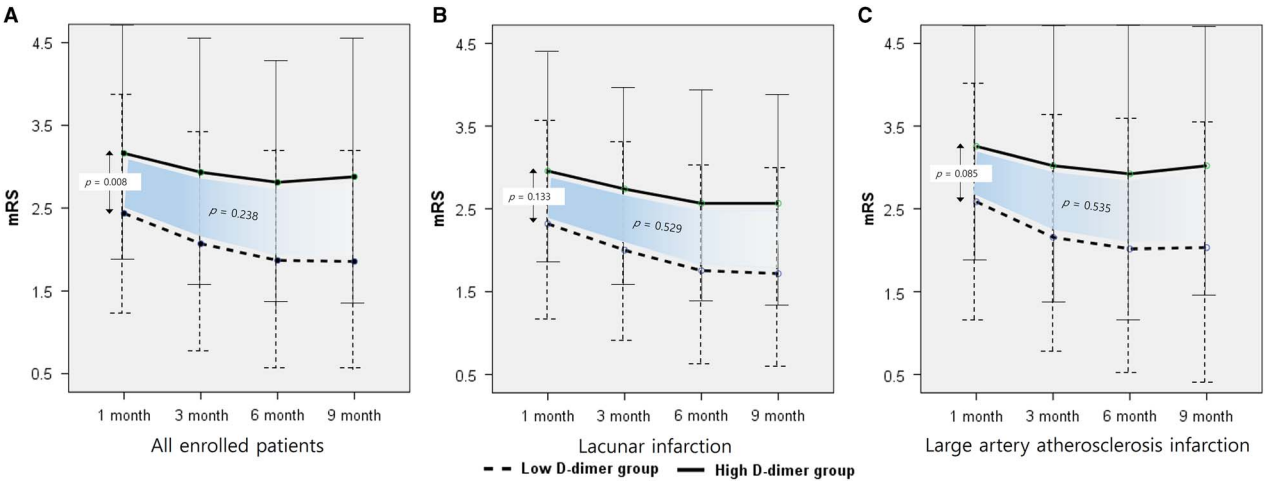

Figure 2: *Changes in the modified Rankin scale (mRS) at the 1-, 3-, 6-, and 9-month follow-ups in all enrolled patients (A) and patients with lacunar (B) and large artery (C) atherosclerosis infarctions. The p values for the main effects of group (shown with bilateral arrows) and group × time interactions are demonstrated. (Time effects are shown in Table 2.)*

statistically significant. Group (p = 0.133), time (p = 0.114), and group × time interaction (p = 0.529, Figure 2B) had no significant effects.

Analysis of Patients With LAA Infarction

There was a strong trend toward a group effect of D-dimer for the entire follow-up period (p = 0.085; p = 0.093 for 1 and 3 months and p = 0.080 for 3, 6, and 9 months in post hoc analysis). A significant effect of time was observed (p <0.001 for the entire period, p <0.001 for 1 and 3 months, and p = 0.039 for 3, 6, and 9 months). However, there were no significant group × time interactions for the entire study period (p = 0.535, Figure 2C).

Discussion

The short- and long-term prognostic roles of D-dimer have been hypothesized, because high D-dimer levels double the risk of acute myocardial infarction in healthy subjects and predict the risk of new events in subjects with coronary heart disease.[17-19] With regard to short-term prognosis, a previous study demonstrated that elevated D-dimer levels were related to stroke severity on admission and poor outcomes at discharge.[8,20] However, several

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studies on D-dimer as a long-term prognostic marker reported conflicting data.[17,21] In a previous study, D-dimer levels were related to the extent of neurological damage and disability.[10] In contrast, other studies found no correlation between D-dimer levels and stroke severity.[17,22,23] Our results are in accordance with latter studies, because once significantly different functional outcomes were set initially depending on the D-dimer levels, longitudinal temporal changes in functional outcomes were not influenced by D-dimer levels (no group × time effect). We showed that D-dimer predicted poor outcomes in the acute (worse initial NIHSS) and subacute (1-month mRS) phases, which is consistent with a previous study in which D-dimer levels were independently associated with stroke progression in the acute phase.[7] However, one study found that D-dimer levels were not associated with stroke severity after excluding venous thrombosis with magnetic resonance direct thrombus imaging.[11] Although our study showed a trend toward a significant association between D-dimer levels and acute stroke severity, further large-scale studies are necessary to clarify this relationship.

The present study also showed that the patients with higher D-dimer levels had significantly worse initial functional outcomes, and these worse outcomes were maintained continuously throughout the 9-month follow-up period compared with the low D-dimer group (group effect). This finding was in line with a previous study showing higher D-dimer levels in patients with severe and moderate residual disability than in patients with absent residual disability.[17]

When analyzed by stroke subtype, this tendency was sustained in patients with LAA infarction, but the power of the group effect was reduced to a strong tendency. D-dimer did not affect initial functional outcomes or longitudinal changes in functional outcomes in patients with lacunar infarction. Regardless of stroke subtype, D-dimer levels had not influenced long-term changes in functional outcomes during the 9-month follow-up period. The significant difference in D-dimer levels between lacunar and LAA infarctions in our study is in accordance with a previous study, in which D-dimer levels were highest in cardioembolic infarction, followed by atherothrombotic and then lacunar infarction, and these differences were statistically significant from one another.[22,24,25]

With respect to long-term effects of D-dimer levels, to the best of our knowledge, this is the first study in which functional outcomes have been serially measured over time in relation to initial serum D-dimer levels by stroke subtypes after acute stroke. Initial D-dimer levels had no influence on changes in the long-term functional outcomes, regardless of stroke subtype. Therefore, D-dimer seems to have implications only for the initial acute phase of stroke, and elevated D-dimer levels can be adopted as a possible surrogate marker for poor functional outcomes at acute and subacute stages.

There are limitations to the present study. We could not exclude the possibility of silent venous thrombosis because we did not routinely perform imaging studies such as leg vein ultrasonography, computed tomography angiogram, or radionuclide lung scan. However, on a daily clinical basis, physicians do not routinely perform these imaging studies for all stroke patients. Therefore, although it is one of the major limitations of this study, it is also a reflection of current clinical practices.

In conclusion, although D-dimer predicted poor outcomes in the acute and subacute phases after noncardioembolic stroke, it had no influence on changes in long-term functional outcomes. Therefore, elevated D-dimer levels can be used as a surrogate marker for poor functional outcomes only during the acute stage. Further evaluation of serum D-dimer levels could be helpful as a predictive marker for stroke prognosis.

Disclosures

The authors do not have anything to disclose.

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