# D-dimer levels in young patients with ischemic stroke: A clinical report

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**Summary**

*Objective:* This clinical report investigates the role of D-dimer in young ischemic stroke patients and its association with stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) and functional outcomes evaluated using the modified Rankin Scale (mRS). *Subject and method:* We conducted a prospective study on 35 young patients (aged under 46) diagnosed with acute ischemic stroke at 108 Military Central Hospital in Ha Noi from October 2022 to April 2023. Each patient underwent thorough clinical evaluation, including a detailed medical history, physical examination, and neuroimaging studies. D-dimer levels were measured within 24 hours of admission using standard laboratory assays. The patients were divided into 2 groups according to mRS scores or NIHSS scores evaluated on the first day inhospital. *Result:* We observed that plasma D-dimer level correlated significantly with the prognosis of acute cerebral infarction (ACI) evaluated based on both mRS scores (1526.58 ± 1462.51ng/mL for poor prognosis versus 348.22 ± 201.14ng/mL for good prognosis, $p<0.05$) and NIHSS scores (1962.00 ± 1578.50ng/mL for poor prognosis versus 501.93 ± 663.10ng/mL for good prognosis, $p<0.05$). *Conclusion:* Our results demonstrated that there is a significant correlation between elevated D-dimer levels and worsened functional outcomes and increased mortality in young patients with acute ischemic stroke.

*Keywords:* Acute cerebral infarction, D-dimer, biomarker, young stroke, NIHSS score, mRS score, pronosis.

## 1. Background

Ischemic stroke in young adults is becoming a severe public health burden due to high health-care costs and loss of labor productivity [1]. In contrast with the decreasing incidence of stroke in older adults, an increasing incidence of ischemic stroke in young adults has been reported in recent years [2]. While traditionally considered a condition of the elderly, there is a growing recognition of ischemic stroke in the young adult population. The pathophysiology of stroke in this demographic presents unique challenges due to its diverse etiologies, including cardioembolism, arterial dissection, and hypercoagulable states.

D-dimer, a product of fibrin degradation, is actually a reflection of disturbances in coagulation-fibrinolysis system. The plasma D-dimer level increases during blood thrombosis and degradation of fibrin, therefore plasma D-dimer could be a biological marker of haemostatic abnormalities and thrombosis. Elevated plasma D-dimer levels are reportedly a determinant of stroke progression, infarction volume and the incidence of stroke in cases of acute ischemic stroke. In addition to being resistant to ex vivo activation, relatively stable, D-dimer has a long half- life, and plasma D-dimer levels can be tested inexpensively and easily with standard laboratory equipment [3]. Many studies have investigated whether plasma D-dimer levels are determinant of poor functional outcomes after acute ischemic stroke, however, the conclusions of

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the studies were controversial. Recently, several studies indicated that high D-dimer levels were not only associated with high risk of poor outcome and mortality [4] but also progressing ischemic stroke [5]. The present study was conducted to assess D-dimer levels in young stroke patients, aiming to unravel its associations with neurological severity and functional outcomes, as quantified by the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS), respectively.

## 2. Subject and method

From October 2022 to May 2023, our prospective cohort study recruited 35 participants (age under 46 years) who were diagnosed with AIS at the Department of Stroke, 108 Military Central Hospital, Ha Noi, Viet Nam. Diagnosis of ischemic stroke was made according to World Health Organization criteria [6] confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI). Additional exclusion criteria were as follows: (1) Diagnosis of AIS with malignant tumor, pulmonary embolism, deep venous thrombosis (DVT), hematopathy or pregnancy, diseases or specific pathological/physiological conditions that possibly affect D-dimer level; (2) Time from stroke onset to admission under 72 hour; (3) Modified Rankin Scale (mRS) score ≥ 3 before stroke onset, and (4) missing data on admission D-dimer level or additional laboratory parameters. Finally, a total of 35 patients were potentially eligible for this anaysis. Venous sampling for quantitative measurement of D-dimer was taken at the time of admission. Values less than 500ng/ml was considered normal and values equal or more than 500ng/ml were taken as raised D-dimer level. We evaluated the severity of stroke by NIHSS on admission, a tool used to objectively quantify neurological impairment. It includes the following items: Level of consciousness, best gaze, visual fields, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, dysarthria, extinction and inattention. Each item scores a specific ability from 0 to 4. For each item, a score of 0 indicates a normal function, while a higher score is indicative of more impairment. Total NIHSS score is limited from 0 to 42 (the higher the score, the more severe the stroke). The score is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by doctors or nurses. A trained-physician observed the patient's ability to answer questions and perform activities, ratings for each item. NIHSS can be viewed online at http://www.nihstrokescale.org/ [7]. The NIHSS scores yielded 2 categories of stroke severity: NIHSS scores less than or equal to 15 mean good prognosis; NIHSS scores greater than 15 mean poor prognosis.

We evaluated the modified Rankin Scale (mRS) at hospital discharge, splited into two broad categories to simplify the interpretation of outcomes in this study: Good Prognosis (mRS 0-2): This category typically includes patients with no symptoms (mRS 0), those with no significant disability (mRS 1), and individuals with slight disability (mRS 2). Patients in this category are generally able to carry out daily activities independently or with minimal assistance; Poor Prognosis (mRS 3-6): This category often encompasses patients with moderate disability (mRS 3), moderately severe disability (mRS 4), severe disability (mRS 5), and death (mRS 6). Patients in this category may require varying degrees of assistance, ranging from help with walking to constant nursing care, or they may have succumbed to the condition.

Quantitative variables were represented by mean ± standard deviation. Categorical variables were demonstrated as percentages. Student T-test was used to compare Quantitative variables. Associations between the prognosis of stroke and D-dimer level were also assessed using logistic regression models in univariate adjustment including age, gender, hypertension, diabetes, smoking, alcoholic and obesity. $p<0.05$ was considered statistical significance. Analyses were carried out with SPSS software (version 26; SPSS, Chicago, IL).

## 3. Result

From October 2022 to April 2023, we enrolled 35 young ischemic stroke patients under 46 years

according to the study criteria. Table 1 shows the characteristics of the study population.

**Table 1. Characteristics of patients**

| Characteristics | | n (%) |
|---|---|---|
| Sex | Female | 4 (11.4) |
| | Male | 31 (88.6) |
| Age | 18-30 | 3 (8.6) |
| | 31-45 | 31 (91.4) |
| | Mean ± SD | 39.14 ± 5.19 |
| Glasgow (Mean ± SD) | | 13.54 ± 2.45 |
| NIHSS (Mean ± SD) | | 9.85 ± 8.86 |
| mRS (Mean ± SD) | | 2.20 ± 1.76 |
| Smoking | | 12 (34.3) |
| Alcoholic | | 6 (17.1) |
| Obesity | | 10 (28.6) |
| Hypertension | | 4 (11.4) |
| Diabetes | | 4 (11.4) |
| ***Total*** | | ***35 (100.0)*** |

Patient demography: Mean age was 39.14 ± 5.19, with 11.4% women (n = 4), 11.4% hypertension (n = 4), 11.4% diabetes (n = 4), 34.3% smoker (n = 12), 14.3% alcoholic (n = 5), and 28.6% obesity (n = 10). In clinical assessment, Glasgow was 13.54 ± 2.45, and NIHSS and mRS had the mean score were 9.85 ± 8.86 and 2.20 ± 1.76, respectively. There was no detectable cancer patient. In this study, the statistics indicate that patients with hypertension and diabetes have a lower prevalence compared to the older age group. Due to the small sample size, we opted not to conduct a prognostic factor analysis.

**Table 2. Etiology of young ischemic stroke**

| Etiology | Quantity | Percentage (%) |
|---|---|---|
| Large vessel disease | 10 | 28.57 |
| Cardioembolic disease | 7 | 20 |
| Small vessel disease | 6 | 17.14 |
| Other identified causes | 3 | 8.58 |
| Undetermined causes | 9 | 25.71 |
| ***Total*** | ***35*** | ***100*** |

The main causes of stroke in patients were mainly due to large vessel disease (28.57%), cardioembolic disease (20.00%), and undetermined causes (25.71%). For the category of other identified causes, there were 3 patients, with two cases having Moyamoya disease, and one case involving dissection of the cervical arteries.

**Table 3. Clinical characteristics, D-dimer level, and statistical analysis of their associations with ACI patients' prognosis evaluated by mRS score**

| | Poor* n = 12 | Good* n = 23 | Univariate analysis p |
|---|---|---|---|
| Age (n, %) | 39.67 ± 7.04 | 38.87 ± 4.08 | 0.64 |
| Male (n, %) | 10 (83.3) | 21 (91.3) | 0.48 |
| Smoking (n, %) | 5 (41.7) | 7 (30.4) | 0.51 |
| Alcohol (n, %) | 4 (33.3) | 2 (8.7) | 0.37 |
| Obesity (n, %) | 6 (50.0) | 4 (17.4) | 0.05 |
| D-dimer (ng/mL) | 1526.58 ± 1462.51 | 348.22 ± 201.14 | 0.03 |

** Poor (poor prognosis group): mRS score 3-6. Good (good prognosis group): mRS score 0-2. Data are mean ± standard deviation values or the percentage (number) of patients.*

While there were no significant differences in age, gender distribution, smoking, and alcohol consumption between the two groups (p>0.05), there was a trend towards a significant difference in obesity prevalence with p = 0.05.

Mean D-dimer levels in the poor prognosis group was 1526.5ng/mL (±1462.51) but mean D-dimer levels in the good prognosis group was 348.22ng/mL (±201.14). Notably, D-dimer levels are significantly higher in the poor prognosis group compared to the good prognosis group with univariate analysis (t-test) p-value = 0.03.

**Table 4. Clinical characteristics, D-dimer level, and statistical analysis of their associations with ACI patients' prognosis evaluated by NIHSS score**

| | Poor* (n = 6) | Good* (n = 29) | Univariate analysis |
|---|---|---|---|
| | | | p |
| Age (n, %) | 36.33 ± 8.89 | 39.72 ± 4.07 | 0.17 |
| Male (n, %) | 5 (83.3) | 26 (89.7) | 0.66 |
| Smoking (n, %) | 1 (16.7) | 11 (37.9) | 0.34 |
| Alcohol (n, %) | 1 (16.7) | 5 (17.2) | 0.73 |
| Obesity (n, %) | 4 (66.6) | 6 (20.7) | 0.19 |
| D-dimer (ng/mL) | 1962.00 ± 1578.50 | 501.93 ± 663.10 | 0.016 |

** Poor (poor prognosis group): NIHSS score > 15. Good (good prognosis group): NIHSS score ≤ 15. Data are mean ± standard deviation values or the percentage (number) of patients.*

There were no significant differences in age, gender distribution, smoking, alcohol consumption, and obesity between the two groups. Mean D-dimer levels in the poor prognosis group was 1962.00ng/mL (±1578.50) while mean D-dimer levels in the good prognosis group was 501.93ng/mL (±663.10), the univariate analysis (t-test) p-value = 0.016. This was a significant difference in D-dimer levels between the poor and good prognosis groups (p<0.05), with higher levels in the poor prognosis group.

## 4. Discussion

D-dimer as a specific cross-linked fibrin degradation product, is a reliable and sensitive index of fibrin deposition and stabilization. It is usually used as a biomarker for the diagnosis, management and pronosis of a variety of thrombosis related clinical conditions, esspecially in stroke [8]. The elevated D-dimer represents the ongoing thrombus formation in cerebral vessels and may suppress the endogenous fibrinolytic system [9]. As we all know, both thrombosis and inflammation play important roles in the progression of ischemic stroke. Several mechanisms were raised to explain the correlation between elevated D-dimer level and worse outcome in AIS. Elevated D-dimer level may reflect the ongoing thrombus formation in brain vessels [9]. Thus, D-dimer may be a marker of systemic hypercoagulability [5]. Besides, D-dimer may activate the inflammatory process [10]. It was reported that D-dimer could activate monocyte to release proinflammatory cytokines such as interleukin-6 [11]. However, more studies are needed to further address the underlining mechanism.

This study was planned to see the role of D-dimer and its association with severity and prognostic outcome of AIS in young adults by using NIHSS and mRS score. Clinical history was taken in detail, complete general physical and systemic examination was done, taking comorbidities and risk factors into consideration. To our knowledge, this is one of the few studies to assess the effects of D-dimer on stroke severity and adverse functional outcomes after acute ischemic stroke in young adults. Overall, we found that after adjustment for the ACI risk factors like gender, smoking, alcoholic and obesity, only increased D-dimer level remained an independent predictor for poor prognosis and associated with more severe stroke among young ACI patients. Inconsistent with other reports, which have indicated that the poor outcome of acute ischemic stroke patients is associated with age,

gender, life styles, etc [12], [13]; our study could not show that gender, smoking, alcoholic, obesity are risk factors for poor prognosis of ACI patients. The small sample size of our study not allows us to do multifactorial analyses with forementioned risk factors adjustment. This reason increases the reliability of the determination of plasma D-dimer level as the prognosis biomarker for young ACI patients in this study. The study by Sato et al. was only conducted in patients with large vessel occlusion (LVO) [14]. These results are similar to previous studies by Bao et al. and Zhang et al., which stated that an increase in D-dimer is a predictor of worsened clinical outcomes and increased mortality [15], [16]. These results are also similar to a previous study by Nezu et al. which revealed that a high D-dimer was related to the mortality of stroke at hospital discharge. A high D-dimer was an independent factor in all-cause mortality and recurrent stroke in cryptogenic stroke patients [17]. Hutanu et al, revealed that high levels of D-dimer were an independent predictor of poor outcome at 3 months after the onset of ischemic stroke [18].

This study analyzed D-dimer as a predictor of clinical outcomes and mortality in patients under 46 years with acute ischemic stroke. The result found the significant correlation between elevated D-dimer levels and worsened clinical outcomes and increased mortality in young patients with acute ischemic stroke. These result suggest that plasma D-dimer level has a good correlation with the prognosis of acute stroke, and its early and easy availability, shows to be a good candidate of prognosis biomarker for young stroke patients. It will give clinicians an important guide for patient management and will give more reliable information to the patients and family for their better understanding of the course of the disease.

There are some limitations in our study. First, this single-center study was limited partially by its relatively small sample size to carry out more stratification research (e.g. a large sample size can have the multivariate analysis to pronosis young ischemic stroke), which is also the focus and concern that we will explore in the following research, and large scale studies would be expected to further verify conclusions. Secondly, the follow-up period of the study is relatively short, D-dimer should be tested several times in the period of admission and after hospital discharge. Thus, a study on the association between D-dimer and long term outcomes of AIS is needed.

## 5. Conclusion

Our results demonstrated that there is a significant correlation between elevated D-dimer levels and worsened functional outcomes and increased mortality in young patients with acute ischemic stroke. We also wish to be able to give a guidable plasma D-dimer value with adjustment for more stroke risk factors.

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