D-Dimer as a Prognostic Biomarker for Short-Term Functional Outcome in Acute Ischemic Stroke Patients

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Abstract

Background

Acute ischemic stroke (AIS) is one of the major causes of disability and death worldwide. Several factors have been associated with a potentially increased risk of poor outcome after stroke (e.g., advanced age, stroke severity, diabetes, baseline hyperglycemia, etc). Still, the post-stroke clinical outcomes are not easily predicted. In order to improve patient care in the near future, new risk prediction models incorporating the use of specific biomarkers might be helpful.

Objectives

We aimed to investigate the association between D-dimer plasma level and post-stroke outcome.

Methods

80 AIS patients, who admitted to the Neurology Department within 24h of stroke onset and received regular treatment during the period from 2019 to 2021, were included in this prospective, observational cohort study. Stroke severity was evaluated using the National Institute of Health Stroke Scale (NIHSS). For each patient, D-dimer plasma level was evaluated at admission. The functional outcome was evaluated by using a modified ranking scale (mRS) at 30 days post-stroke.

Results

After a 30-day follow-up period, only 15% of AIS patients included in this study had favorable functional outcome, and total of 8 patients (10%) died. There were a significant relationship between high d-dimer levels and poor functional outcome. However, a non-significant association between d-dimer level and mortality was detected.

Conclusion

The plasma D-dimer biomarker can be a simple readily available test and reliable predictor of ischemic stroke functional outcome in union with the common instrumental tests. However, it has no predictive value for mortality.

Keyword

Acute ischemic stroke; D-dimer levels; NIHSS; mRS; Prognosis.

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Introduction

Acute ischemic stroke (AIS) is one of the major causes of disability and death worldwide [1]. Over the last four decades, the stroke incidence in low- and middle-income countries has more than doubled [2]. Stroke is a major health problem in the Egyptian population. Egypt is the most populated country in the Middle East with over 98 million inhabitants. However, there are few demographic stroke studies, mostly obtained through door to door surveys in some governorates [3]. They revealed an overall crude stroke prevalence of 613/10,0000 and crude incidence rate of 202/10,0000 [4].

Given the increased understanding of the pathophysiologic mechanisms of ischemic stroke, many serum biomarkers have been identified in the last decade. These biomarkers include inflammatory, hormonal, hemostatic, oxidative, and metabolic serum markers [5]. Easily attainable, these markers have the potential to provide information related to patient prognosis as the existing neuroimaging and clinical predictors are not always reliable [6].

D-dimer, the ultimate product of plasmin-mediated degradation of fibrin-rich thrombi, has emerged as a simple blood test that can be employed in diagnostic algorithms for the exclusion of venous thromboembolism [7]. For stroke patients, this biomarker can detect disrupted vessels, dissolved clots, and the release of stroke-related tissue factors [8]. D-dimers also serve as a good biomarker because of its prolonged stability, half-life, cost-effectiveness, and high sensitivity (> 97%) [9].To date, only a few individual retrospective cohort studies have attempted to evaluate whether plasma D-dimer levels can predict future functional outcomes and mortality post-stroke [10, 11]. These studies have not established a consensus here. Thus, the purpose of this study was to investigate the association between plasma D-dimer level at admission and short-term functional outcome in Egyptian patients with acute ischemic stroke (AIS).

Methods

Patients and Study Design

All patients who were admitted within 24 hours of experiencing a new focal or global neurological event and received regular treatment in the neurology intensive care unit (ICU) and stroke unit, Zagazig University Hospitals, during the period between February 2019 and February 2021 were included in this prospective study. The patients were diagnosed according to the World Health Organization (WHO) criteria [12]. All patients presented with acute stroke were subjected to CT brain on admission to exclude patients with stroke mimic or primary intracranial hemorrhage. Magnetic resonance imaging (MRI) of the brain was done in suspected brain stem lesions, early ischemic stroke, and when follow-up CT brain is free. Written informed consent was taken from the patients or their family members to participate in the study.

We recorded the medical history prior to the stroke and analyzed the following variables: age, gender, histories of vascular risk factors including hypertension, diabetes mellitus, previous stroke or transient ischemic attacks (TIA), current or former smoking, and hyperlipidemia, obesity (identified by body mass index ≥ 30), ischemic heart disease, and atrial fibrillation (AF), either as a history of AF or AF diagnosed during the index admission by electrocardiography. Baseline glycemia, body temperature, blood pressure levels, complete blood count, liver and kidney function test, coagulation profile, and lipid profile were also recorded. Stroke severity on admission was ascertained by a neurologist experienced in NIHSS. Acute ischemic stroke subtypes were determined by using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [13].

D-dimer Sampling

For each patient, D-dimer level was measured on admission. Plasma aliquots were collected from blood samples centrifuged at 1,500–2,500 g for 15 min at ambient room temperature and analyzed at room temperature within 2 h of blood withdrawal. D-dimer concentration was measured through particle enhanced, immunoturbidimetric method using the COBAS 6000 analyzer (Roche diagnostics, Mannheim, Germany) in the range of 0.15– 9.00 μg fibrinogen equivalent/mL (μg FEU/mL). Measurements outside this range were considered to be below the lower limit or above the upper limit of detection of the assay. The laboratory reference range for D-dimer test was < 0.5 μg FEU/mL.

Outcome measures

Our study evaluated functional outcome as assessed on the modified Rankin scale (mRS) at 30 days after stroke onset, via telephone or face to face by a neurologist. A good functional outcome was defined as mRS of 0-2 points, whereas a poor outcome was defined as mRS ≥ 3 points [14].

Statistical analysis

All data were collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test or Mann Whitney, paired by paired t or Sign test. P value was set at <0.05 for significant results and <0.001 for highly significant results.

Results

Table 1 shows demographic and baseline characteristics among studied population. The mean age of our patients was 69.3± 11.6 with 63.7% male predominance. Hypertension was the most common risk factor of AIS followed by DM and AF (75%, 55%, and 31.3%, respectively). The mean of NIHSS on admission was 12.4±4.9. According to TOAST criteria, large artery atherosclerosis was the most common stroke subtype in our study followed by cardioembolic stroke (57.5% and 26.3%, respectively).

Table 2 shows that only 15% of our patients had favorable functional outcome at 30 days post-stroke. While, the all-cause mortality rate was 10%.

Table 3 shows that d-dimer level was significantly higher among patients with poor functional outcome at 30 days post-stroke, however, no statistically significant difference was detected regarding 30-day mortality.

Table (1) Demographic and Clinical characteristics of studied population:

	AIS patients, N=80
Demographic data	
Age (Mean ± SD)	69.3± 11.6
Gender, n(%)	
Female	29(36.3%)
Male	51(63.7%)
Risk factors	
Hypertension, n (%)	60(75%)
Diabetes, n (%)	44(55%)
AF, n (%)	25(31.3%)
Ischemic heart, n (%)	20(25%)
Smoking, n (%)	17(33.3%)
Obesity (BMI≥30), n (%)	35 (43.7%)
Hyperlipidemia, n (%)	32(40%)
Previous stroke, n (%)	10(12.5%)
Previous TIA, n (%)	12(15%)
Clinical data	
SBP (Mean ± SD)	155.94 ± 24.01
DBP (Mean ± SD)	94.0 ± 12.26
RBS (Mean ± SD)	169.7 ±71.2
Body temperature (Mean ± SD)	37.1± 0.5
Admission NIHSS (Mean ± SD)	12.4±4.9
Stroke subtypes (TOAST criteria)	
Large artery atherosclerosis, n (%)	46(57.5%)
Cardioembolic, n (%)	21(26.3%)
Small artery, n (%)	8(10.0%)
Undetermined, n (%)	5(6.2%)

P > 0.05 = non-significant
SD=standard deviation, AF=atrial fibrillation, BMI=body mass index, TIA=Transient ischemic attack, SBP=systolic blood pressure, DBP=diastolic blood pressure, RBS=random blood sugar, NIHSS= National Institute of Health Stroke Scale TOAST=trial of ORG 10172 in acute stroke treatment, h=hours

Table 2 Outcome at 30 days post-stroke

Outcome	**AIS patients,N=80**
mRS at 30 days	
Favorable (mRS ≤ 2), n(%)	12(15%)
Unfavorable (mRS >2), n(%)	
Mortality, n(%)	68(85%)

	8 (10%)

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant
NIHSS= National Institute of Health Stroke Scale, ICH=intracerebral hemorrhage, mRS= modified rankin scale

Table 3 Relationship between D-Dimer level and post-stroke outcome at 30 days

Laboratory Biomarker	**Good outcome** (mRS ≤ 2)	**Poor outcome** (mRS > 2)	**P value**
D-Dimer, μg/mL. *Mean ± SD*	2.3±1.5	2.8±1.7	**0.03***
	No mortality	**Mortality**	
	1.9±1.0	2.0±1.1	0.57

*p<0.05 is statistically significant
SD=standard deviation, mRS= modified rankin scale

Discussion

Acute ischemic stroke (AIS) is one of the major causes of disability and mortality worldwide. Several factors have been associated with a potentially increased risk of post-stroke poor outcome (e.g., advanced age, male gender, stroke severity, diabetes, baseline hyperglycemia, etc)[15] . Still, the clinical outcomes are not easily predicted as most of the current clinical and radiological risk scores are non-specific and have modest predictive value [16].

Regarding risk factors of ischemic stroke; this study reported that the most common risk factors in were hypertension (75%), diabetes mellitus (DM) (55%), and atrial fibrillation (AF) (31.3%) %, respectively. However, in a recent Egyptian study conducted by **Aref et al.,** DM was the most prevalent risk factor, followed by hypertension, and followed by dyslipidemia [17].

Our results demonstrated that only 15% of our patients had good functional outcome (mRS 0-2) at 30 days post-stroke versus 85% had poor outcome. **Ghosh et al**. reported that 70 %of AIS received regular treatment had poor functional outcome at 30 days post-stroke [18].While, **Bielewicz et al.** reported 28.88% had good functional outcome at 3 month follow-up by mRS[19]. The variation in improvement rates between studies may be due to the differences in mean ages, initial NIHSS as well as the variability in the time of follow up. Regarding post-stroke mortality rate, his current study revealed that within 30 days after stroke onset , a total of 8 patients (10%) expired.

D-dimer is a fibrin degradation product (FDP) that is present in blood after a blood clot is degraded by fibrinolysis. Thus, it is a global indicator of coagulation activation and fibrinolysis [20].This study demonstrated that a significantly higher levels of D-dimer on admission were associated with poor functional outcome of AIS patients after 30 days. However, a non-significant relationship between D-dimer level and mortality was detected. Our findings are in line with many previous studies like **Ghosh et al., Melake et al.,** and **Kim et al.** [18,21,22] which evaluated D-dimer as marker for poor prognosis in AIS. On the other hand, other investigators found no such correlations between D-dimer levels and stroke outcome and mortality [23,24,25]. Higher D-dimer levels mean greater

chance of having a large infarct, poor response to treatment or thromboembolic events such as stroke progression. There is also some evidence that some markers of hemostatic function are acute phase reactants; d-dimer is one of these markers, which may act to stimulate the inflammatory process. All of these reasons could result in unfavorable outcome [26].

In practice, the application of d-dimer as a predictor of functional outcome has several advantages including its high resistance to ex-vivo activation and relatively long half-life [27]. It is rarely elevated in healthy people [28], and its measurement is inexpensive and can be easily and routinely performed in ordinary laboratories.

Conclusion

The plasma D-dimer biomarker can be a simple readily available test and reliable predictor of ischemic stroke functional outcome with no predictive value regarding post-stroke mortality.

Declarations

Funding: The authors did not receive any compensation for the manuscript.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical standard statement: We have obtained consent and permission from patients or relatives to participate in this study. The study was approved by institutional review board (IRB) of Zagazig University.

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