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Original Research Article

The Association between Elevated D-Dimer Levels and Heightened Ischemic Stroke Risk in Non-Valvular Atrial Fibrillation Patients: A Retrospective Study

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Abstract

Objective: This study looked at the association between elevated D-dimer levels and the ischemic stroke risk in order to determine whether these levels could be a predictive ischemic stroke risk factor in individuals with non-valvular atrial fibrillation (NVAF).

Methods: The NVAF patients participating in this retrospective single-center study had not received anticoagulant treatment. Two groups of patients were identified: those who had experienced an ischemic stroke and those who had not. A thorough examination of the patients' medical records, clinical and demographic evaluations, and an overview of the test results were all part of the study.

Results: This investigation included 105 NVAF in-patients (68 men, 37 women, median age 74.18±9.46 years) who were eligible and had not been treated with anticoagulants. 26 patients had acute ischemic stroke. D-dimer levels improved with age and correlated positively (P <0.001) with stroke risk scores, such as CHADS2 and CHA2DS2-VASC. Even after controlling for gender and age, the connection remained substantial (P<0.001). Stroke patients had significantly higher baseline D-dimer levels (1.24 vs. 0.60 mg/L, P<0.001), although there was no relevant difference between the two groups (0.60 vs. 0.56 mg/L, P= 0.320). Logistic regression study identified D-dimer levels on stroke onset and OMI as independent ischemic stroke risk factors (P<0.001), while the rise from baseline did not predict stroke likelihood (P=0.125).

Conclusion: D-dimer levels were favorably connected with ischemic stroke risk classification in NVAF patients, but not with actual occurrence. Although elevated D-dimer levels do not predict ischemic stroke in this patient population, the study did find a possible correlation between them and stroke risk factors.

Recommendation: Further research is needed to explore additional factors contributing to ischemic stroke risk in NVAF patients and to identify more robust predictive markers for this specific population.

Keywords: Ischemic Stroke, D-dimer, Non-Valvular Atrial Fibrillation, Risk Stratification, Risk Factor

Introduction

With a prevalence of 0.5% to 2% of the population, atrial fibrillation (AF) is a common cardiac arrhythmia illness that significantly raises the risk of stroke and mortality, especially in Western Europe and North America [1]. AF exhibits an increased incidence as individuals advance in age, and concomitantly, the geriatric demographic witnesses a surge in the prevalence of AF cases. Roughly 10% of people 80 years of age and older are thought to experience this degenerative condition [2]. The optimal management of AF is of utmost importance, considering its significant association as an autonomous stroke risk factor. The evaluation of thromboembolic risk and the implementation of suitable prophylactic measures are essential components in the management of

atrial fibrillation. Presently, risk assessment tools that have gained widespread acceptance in the medical community, such as the CHADS2 and CHA2DS2-VASc scores, serve to facilitate the evaluation of stroke risk. These tools take into account various factors, including but not limited to vascular disease, gender, and age, with particular emphasis on individuals aged 65 to 74 years [3, 4].

D-dimer, a biomarker indicative of the process of thrombus formation and subsequent fibrinolysis, exhibits an inclination to increase in correlation with advancing age and is frequently observed to be elevated in individuals diagnosed with AF. The patient's condition falls within the range of 7-9 on the medical scale. Recent studies have established a correlation between elevated levels of D-dimer and B-type natriuretic peptide (BNP), a biomarker associated with cardiac function [5]. Significantly, there exists a correlation between heightened levels of D-dimer and an escalated susceptibility to clot-related occurrences, including myocardial infarctions and aortic dissections, particularly in individuals diagnosed with atrial fibrillation and presenting with other cardiovascular risk factors [6].

This study's primary goal was to clarify the association between D-dimer levels and the likelihood of non-valvular atrial fibrillation (NVAF) patients experiencing an ischemic stroke. The aim of this investigation was to evaluate the possibility of increased D-dimer levels serving as a predictive indicator for an increased risk of stroke within the specified patient group.

Methodology

Study Design: This was a single-centered retrospective study.

Study Setting: The study was conducted at 'Bhima Bhoi Medical College' between 'October 2022 to March 2023'.

Participants: This study included patients with atrial fibrillation (AF).

Ethical Consideration: The Ethics Committee permitted the study, and each participant gave written informed permission.

Inclusion Criteria: Patients presenting with a diagnosis of nonvalvular atrial fibrillation (NVAF), either established prior to hospital admission or identified during the course of hospitalization, as confirmed by ECG/Holter monitoring and echocardiography. The study cohort comprised of people aged 50 yrs or older. Patients who were not administered anticoagulation therapy, such as warfarin or novel oral anti-coagulants like dabigatran or apixaban.

Exclusion Criteria:

Individuals suffering from sepsis, aortic dissection (AD), acute myocardial infarction (AMI), severe pneumonia, heart failure (HF), venous thrombosis, chronic or acute pulmonary embolism (PE), and hepatic or renal impairment. Individuals who have recently undergone surgery or sustained an injury. cancer patients who had chemotherapy or radiation therapy. individuals with hematological conditions.

Ischemic Stroke Diagnosis: A neurologist's clinical examination was used to diagnose individuals with an ischemic stroke, and CT or MRI scans were used to confirm the diagnosis. Both acute and recurrent ischemic strokes were included in this diagnosis.

Clinical Variables: Age, gender, laboratory blood biomarkers (cholesterol, glucose, creatinine, uric acid [UA], and C-reactive protein [CRP]), and medical history were all included in the patient data at baseline. The CHADS2 and CHA2DS2-VASc scores were used to calculate the risk of stroke. D-dimer levels were assessed at six months and a year following the stroke, as well as at baseline (at least a year prior to the beginning of the stroke) and within six to eighty-eight hours of the stroke.

Blood Sample Collection and Assays: The morning following admission, blood samples were obtained from patients and controls, and they were processed in two hours. The immunoturbidimetric technique was used to measure the amounts of plasma D-dimer. The threshold was typically ≤1.0 mg/L. In the hospital's Clinical Laboratory Center, certain blood samples were examined in accordance with the manufacturer's guidelines.

Statistical Analysis: Continuous variables were presented as mean ± SD. At $P < 0.05$, statistical significance was established. Version 17.0 of IBM SPSS Statistics was employed to analyze the data.

Result

This investigation included 105 consecutive in-patients with NVAF, who were above 50 years of age and not on anticoagulant therapy. Of them, 26 had experienced a stroke previously. The patients had a median age of 74.18 ± 9.46 years, with 68 males and 37 females. There was no relevant difference in the baseline D-dimer values between these individuals (0.58 vs. 0.54, P =0.839). The CHADS2 and CHA2DS2-VASc scores were used to evaluate the risk of stroke; greater scores were correlated with D-dimer levels.

Table 1: Basic clinical features of NVAF patients.

Variables	Stroke	No stroke	P value
Age	74.64 ± 4.26	74.03 ± 9.82	0.017
Female (%)	40.02 (31)	33.69 (84)	0.311
SBP, mm Hg	140.88 ± 18.07	132.42 ± 17.35	0.793
DBP, mm Hg	80.12 ± 11.20	75.43 ± 10.85	0.963
Cr, μmol/L	83.98 ± 28.62	93.55 ± 59.84	0.148
GLU, mmol/L	4.70 ± 1.88	4.52 ± 1.70	0.230
TC, mmol/L	4.10 ± 1.73	4.18 ± 0.94	0.207
TG, mmol/L	1.30 ± 0.71	1.35 ± 0.87	0.434
LDL-C, mmol/L	2.30 ±0.80	2.31 ± 0.85	0.240
HDL-C, mmol/L	1.07 ± 0.23	1.15 ± 0.37	0.002
UA, mmol/L	302.03 ± 101.86	348.62 ± 100.08	0.901
LA diameter, mm	42.41 ± 4.29	42.45 ± 6.31	0.305
EF (%)	59.55 ± 7.79	63.12 ± 5.32	0.114
HT (%)	80.65 (62)	83.90 (207)	0.387
CHA2DS2-VASc	3.72 ± 1.38	2.90 ± 1.16	<0.001
CHADS2	1.63 ± 0.84	2.30 ± 1.2	<0.001
DM (%)	33.62 (26)	31.24 (78)	0.698
OMI (%)	15.67 (12)	6.43 (15)	0.005

DM- diabetes mellitus, EF- ejection fraction, DBP- diastolic blood pressure, LA- left atrial, GLU- glucose, HT- hypertension, , HDL-C- high-density lipoprotein cholesterol, LDL-C-low density lipoprotein cholesterol, NVAF- non-valvular atrial fibrillation, OMI- old myocardial infraction, TC- total cholesterol, TG- triglyceride, SBP- systolic blood pressure, UA- uric acid.

Additionally, rising with age, D-dimer levels showed a favorable correlation with CRP levels. Following age and gender adjustments, the sample consisted of 24 stroke cases and 24 non-stroke patients. The baseline D-dimer level differences were not statistically significant (0.60 ± 0.24 vs. 0.56 ± 0.20 mg/L, P =0.320).

D-dimer levels in stroke patients were relevantly higher than baseline (1.24 ± 0.81 vs. 0.60 ± 0.24 mg/L, P <0.001). Five of them experienced repeated strokes, however the difference was not statistically relevant (P =0.340). D-dimer levels were greater in instances of cardioembolic stroke at the beginning (1.58 ± 0.67 vs. 1.05 ± 0.54 mg/L, P =0.507). After a year, D-dimer levels almost reached baseline, although they were still increased after six months.

There were no notable D-dimer changes from baseline in stroke patients who had previously experienced one. D-dimer levels at the outset of the stroke and OMI were independently linked with stroke, although DM, HT, and baseline D-dimer levels were not, according to multivariate analysis. Based on the ROC curve, the study was unable to determine a cut-off value for D-dimer in stroke prediction.

Discussion

The researchers were unable to establish whether a high D-dimer level was a separate risk factor for ischemic stroke in patients with NVAF. However, among NVAF patients, D-dimer levels were linked to the classification of ischemic stroke risk.

D-dimer is a biomarker that is frequently used to screen for diseases including pulmonary embolism and aortic dissection [7]. It represents coagulation and fibrinolysis activation. Research has demonstrated that D-dimer levels can be greater in cardioembolic ischemic stroke and typically rise during acute stroke [8]. Although there were more D-dimer levels in cardioembolic stroke cases in this investigation, statistical significance was limited by the small sample size. Additionally, D-dimer levels have been linked to acute stroke in prospective trials, indicating that it may be a useful short-term prognostic marker [9]. D-dimer levels, however, were not discovered to be connected to stroke recurrence.

However, the CHADS2 and CHA2DS2-VASc scores, which are used to estimate stroke risk in patients with NVAF, showed a favorable correlation with baseline D-dimer levels, according to the study [10, 11]. This suggests a connection between the categorization of ischemic stroke risk and D-dimer levels. The study noted that the CHA2DS2-VASc score would be more appropriate for low-risk individuals with NVAF and verified the association between D-dimer levels and ischemic stroke risk stratification.

The predictive rate of D-dimer levels on cardiovascular events and thromboembolic in atrial fibrillation patients has been studied in the past [12, 13]. While some research offered cutoff values for

event prediction, others stated that D-dimer levels might be utilized to eliminate left atrial thrombus [14]. Unfortunately, the current study was unable to determine an appropriate cutoff value or demonstrate a correlation among baseline D-dimer levels and prevalence of stroke due to the limited study size and retrospective approach. The research took into account a 0.5 mg/L D-dimer threshold value [15].

Conclusion

D-dimer levels show a confident correlation with stroke risk satisfaction and an age-related rise. It is crucial to remember that they are unable to forecast the likelihood of an ischemic stroke in NVAF patients. The study demonstrated the connection between inflammation and D-dimer levels by demonstrating their positive correlation with C-reactive protein (CRP). This association between D-dimer levels and inflammation raises the possibility that thrombosis, AF, and inflammation are related. To validate these results and determine the value of D-dimer levels in predicting the risk of an ischemic stroke in individuals with non-vertically aligned arteries, further extensive prospective investigations are required.

Limitations: There are important limitations to this research: First, there was bias in gender selection because our hospital admitted more men than women with AF and discovered more valvular abnormalities in women. As a result, we might not be able to pinpoint the important female gender-ischemic stroke/TE associations. This retrospective analysis was conducted by a single facility. Since every subject was an inpatient, some preadmission data were missing. illnesses paired with individuals. Selection bias was an issue, and there was no discernible contrast. HT and DM did not increase the risk of an ischemic stroke because most patients had several medical conditions. Above all, there were not many patients or incidences in the study. More extensive, multicenter research is required to validate these results.

Recommendations: Additional investigation is warranted to delve into supplementary variables that contribute to the risk of ischemic stroke in patients with NVAF and to ascertain more resilient prognostic indicators for this particular cohort.

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List of abbreviations:

AD - aortic dissection
AF - atrial fibrillation
AMI- acute myocardial infarction
CAD- coronary artery disease
CHF- congestive heart failure
CRP- C-reactive protein
DBP- diastolic blood pressure
DM- diabetes mellitus
EF- ejection fraction
HC- hypercholesterolemia
HF- heart failure
HT- hypertension
LA- left atrial
LAE- Left atrial enlargement
MI- myocardial infarction
NVAF- nonvalvular atrial fibrillation
OGTT- oral glucose tolerance test
OMI- old myocardial infarction
PE- pulmonary embolism
ROC- receiver operator characteristic
SBP- systolic blood pressure
SD- standard deviation
TEE- transesophageal echocardiography
UA- uric acid.

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