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Evaluation of the relationship between thromboembolic risk score (CHA_2DS_2-VASc) and inflammation and coagulation markers in patients with non-valvular atrial fibrillation in emergency department.

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Abstract

Objective: To evaluate the relationship between CHA_2DS_2-VASc score and inflammation and coagulation markers in patients admitted to Emergency Department (ED) with non-valvular Atrial Fibrillation (AF).

Methods and Results: Eighty-four patients with non-valvular AF were included in the study. CHA_2DS_2-VASc scores were calculated for these patients. In addition, plasma levels of BNP, hs-CRP, CRP, vWF and D-dimer were measured. The relationship between CHA_2DS_2-VASc score and these parameters were evaluated. Eleven (13%) patients were considered to be at low-risk due to CHA_2DS_2-VASc score being<2 and 73 (87%) patients were considered to be at high risk due to CHA2DS2-VASc score being ≥ 2. The mean age of patients was 68 ± 13 years and 50 (60%) of patients were male. Plasma BNP, hs-CRP, CRP, vWF and D-dimer levels were significantly higher in high-risk group. In addition, a significant positive correlation was found between CHA_2DS_2-VASc score and BNP (r=0.436, p<0.001), D-Dimer (r=0.356, p=0.003), hs-CRP (r=0.335, p=0.002), CRP (r=0,331, p=0.002), vWF (r=0.330, p=0.002) and patient age (r=0.573, p<0.001).

Conclusion: It was found that BNP, hs-CRP, CRP, vWF and D-dimer levels increase significantly and that there is a positive correlation between CHA_2DS_2-VASc and these markers in high-risk patients with CHA_2DS_2-VASc score ≥ 2.

Keywords: Atrial fibrillation, BNP, CHA_2DS_2-VASc score, D-Dimer, hs-CRP, vWF.

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Introduction

Atrial Fibrillation (AF), seen in 1-2% of the general population, is the most common arrhythmia among cardiac arrhythmias and causes five-fold increase in the risk of stroke. The prevalence of AF is expected to double due to aging of the population [1-3]. Studies are being conducted towards the use of clinical classification and certain biochemical markers to determine the risk of stroke in patients with AF [4]. CHA_2DS_2-VASc classification is one of the classifications made to demonstrate the risk of stroke development. CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥ 75 years (double), Diabetes Mellitus, Prior Stroke or TIA or thromboembolism (double), Vascular disease, Age 65-74 years, Sex category (female)] classification is a scoring table, recommended at the 2010 European Society of Cardiology (ESC) Management of Atrial Fibrillation guideline for use in determining the treatment and risk of thromboembolism in patients with non-valvular AF, including many up to date risk factors and a scoring scheme ranging between 0 and 9 points. Oral anticoagulation therapy (OAC) is recommended in patients with CHA_2DS_2-VASc score ≥ 2, unless there is a contraindication [5].

Brain Natriuretic Peptide (BNP), C Reactive Protein (CRP), plasma von Willebrand Factor (vWF) and plasma D-dimer levels have been used to evaluate cardiovascular functions and determine the risk of thrombosis in many cardiovascular diseases such as heart failure, atherosclerotic heart disease [6-12]. Plasma BNP levels have been found to be very sensitive in identifying left ventricular dysfunction in patients with Congestive Heart Failure (CHF) and increased BNP levels

have been reported with increased severity of left ventricular dysfunction [6]. BNP level has also been found to be associated with atrial pressure increase [7]. CRP, an acute phase reactant synthesized in the liver, is one of a very sensitive marker of acute and chronic inflammation. Due to studies indicating increased levels of hs-CRP in Coronary Artery Disease (CAD), the role of hs-CRP in the ethiopathogenesis of other cardiovascular diseases has been investigated. As a result of the studies, chronic inflammation has been reported to be effective in the ethiopathogenesis of AF [4].

Elevated plasma vWF levels has been shown in inflammatory and atherosclerotic vascular diseases, in which there is the possibility of endothelial damage [8]. Plasma D-Dimer levels, best biochemical markers of coagulation activity [9], shows the prothrombotic state and thromboembolic risk [10]. It has been stated that D-dimer level increases in the presence of left atrial thrombus and that it is correlated with the volume of thrombus [11]. Although the clinical classifications and biomarker levels were investigated separately in the development of thrombosis, there are not enough studies found in the literature that investigate the relationship between CHA_2DS_2-VASc score and inflammation and coagulation markers. Therefore, we aimed to evaluate the relationship between CHA_2DS_2-VASc score and inflammation and coagulation markers in patients who admitted to emergency department with non-valvular AF.

Materials and Method

The study was initiated following obtaining the approval of the local ethics committee and 84 patients, who were admitted to Emergency Department (ED) with non-valvular AF, were included. Biochemical tests, cardiovascular disease history, risk factors, waist circumference, height measurements and physical examinations of the patients were performed in a detailed manner. Patients with the following characteristics, which may cause contradictions in determining the relationship between CHA_2DS_2-VASc score and inflammation and coagulation markers and determining the CHA_2DS_2-VASc score, were excluded from the study:

1. History of previous venous or systemic thromboembolism in the last 3 months
2. History of valvular heart disease and prosthetic heart valve
3. Patients on Warfarin
4. History of previous myocardial infarction in the last 3 months
5. History of previous inflammatory or infectious disease in the last 1 month
6. History of previous surgery in the last 3 months
7. Patients with a history of malignancy
8. Patients under 18 years of age
9. Patients with connective tissue disease
10. Patients with a history of active tuberculosis (TB)
11. Patients with a history of hyperthyroidism and hypothyroidism

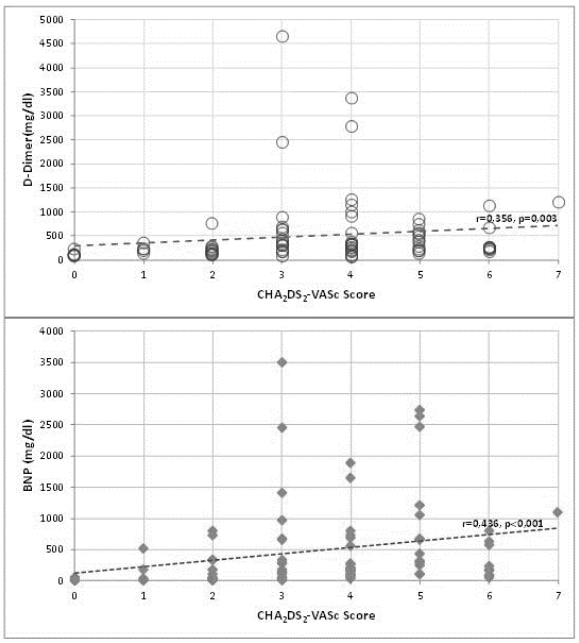

Figure 1. *The correlation between CHA_2DS_2-VASc score and D-dimer, BNP.*

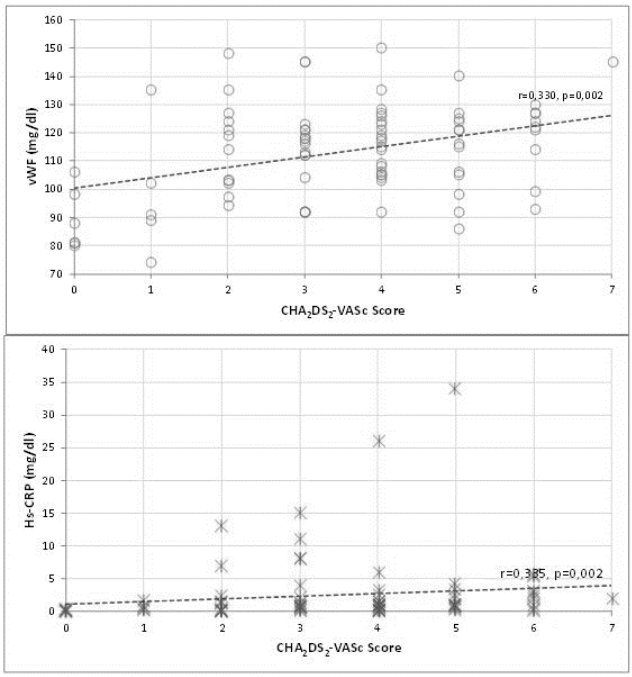

Figure 2. *The correlation between CHA_2DS_2-VASc score and vWF, hs-CRP.*

The points were summed up according to the criteria in CHA_2DS_2-VASc scheme and CHA_2DS_2-VASc score of each patient was calculated, ranging from 0 to 9. Patients were divided into two groups, as high-risk group with score ≥ 2 and as low-risk group with score<2. AF diagnosis was made by clinical signs and marked irregular RR intervals and absolute absence of P waves on electrocardiogram. In order to detect the presence of atrial thrombi, all patients in the study underwent transthoracic echocardiography. Blood samples were collected

from the antecubital veins into VACUETTE® gel vacuum tubes (Greiner Bio-One, Austria). Plasma samples were stored at -70 °C, no more than 6 months. BNP concentrations were determined with IMMULITE® 2000 immunoassay system (Siemens, Germany) by electrochemiluminescence immunoassay (ECLIA) method.

Normal range for BNP was 0-100 pg/ml. vWF and D-dimer levels were measured with AMAX 190® coagulometer (Sigma Diagnostics, UK) by using an immuno-turbidimetric method. Normal ranges for D-dimer and vWF were 0-250 ng/ml and 60-150%, respectively. hs-CRP was measured with IMMAGE® immunochemistry system (Beckman Coulter, USA). The lower limit of hs-CRP detection was 0.2 mg/L. SPSS 15.0 statistical software package was used for the evaluation of variables and tests. While numerical variables with normal distribution and without normal distribution were expressed as mean ± standard deviation and median (minimum-maximum), respectively, categorical variables were expressed as percentage. Analysis of variance (ANOVA) method was used for the comparison of the mean in numerical variables with normal distribution. Mann-Whitney U test was used for the comparison of the median in the numeric variables without normal distribution. Spearman's Rank Correlation was used for two-way analysis and linear regression analysis was used for multivariate analysis of factors affecting the CHA_2DS_2-VASc score. $p < 0.05$ was considered significant in statistical analysis.

Table 1. *The demographic characteristics of patients.*

Data	Patients with low-risk (CHA_2DS_2-VASc score<2)	Patients with high-risk (CHA_2DS_2-VASc score ≥ 2)
N (F/M)	11 (2/9)	73 (48/25)
Age (Mean ± SD)	49 ± 9.78	71 ± 10.48
Hypertension (n (%))	1 (1.2%)	64 (76.2%)
Diabetes (n (%))	0 (0%)	22 (26.2%)
Heart Failure (n (%))	1 (1.2%)	18 (21.4%)
Previous CVA (n (%))	0 (0%)	12 (14.3%)
CAD (n (%))	1 (1.2%)	32 (38.1%)
Smoker (n (%))	8 (9.5%)	15 (17.9%)
Alcohol use (n (%))	2 (2.4%)	0 (0%)

Results

In the study, 50 (60%) of 84 patients were male and the mean age of patients was 68 ± 13 years. CHA_2DS_2-VASc score was found to increase with increased age ($r=0.573$, $p<0.001$). Hypertension, diabetes mellitus, CAD, previous Cerebrovascular Accident (CVA) and CHF was present in 77.4%, 26.2%, 39.3%, 14.3% and 22.6% of patients, respectively. Twenty-seven point four percent of patients were smokers and 2.4% were alcohol users (Table 1). While 12 (14.3%) patients had paroxysmal AF, 72 (85.7%) had permanent AF. The number of patients based on CHA_2DS_2-VASc scores was determined as follows: 0 (n=6), 1 (n=5), 2 (n=12), 3 (n=17), 4 (n=21), 5 (n=13), 6 (n=9) and 7 (n=1). Significant positive correlation was found between CHA_2DS_2-VASc score and BNP ($r=0.436$, $p<0.001$), D-Dimer ($r=0.356$, $p=0.003$), hs-CRP ($r=0.335$, $p=0.002$), CRP ($r=0.331$, $p=0.002$) and vWF ($r=0.330$, $p=0.002$) (Figure 1 and Figure 2). Patients were divided into 2 groups according to CHA_2DS_2-VASc scores. Eleven (13%) patients were found to be at low-risk and 73 (87%) patients were found to be at high-risk. Plasma BNP ($p<0.001$), D-Dimer ($p=0.008$), plasma hs-CRP ($p=0.002$), CRP ($p=0.003$) and vWF ($p<0.001$) levels of patients with high-risk were statistically significantly higher compared to low-risk group (Table 2). Multivariate linear regression analysis of inflammation and coagulation markers that affect CHA_2DS_2-VASc score revealed only BNP (beta=0.372, T=3.562, p=0.001) and vWF (beta=0.216, T=2.066, p=0.042) as independent correlates.

Table 2. *Inflammation and coagulation markers in low and high-risk patients.*

Parameters	Patients with low-risk (CHA_2DS_2-VASc score<2)	Patients with high-risk (CHA_2DS_2-VASc score ≥2)	P
N (F/M)	11 (2/9)	73 (48/25)	-
BNP (mg/dl)	12 (3-518)	250 (8,5-3500)	<0.001
vWF (mg/dl)	89 (74-135)	118 (86-150)	<0.001
D-Dimer (mg/dl)	129 (76-349)	287 (66-4637)	0.008
hs-CRP (mg/dl)	0,3 (0,1-1.7)	1,0 (0.3-34)	0.002
CRP (mg/dl)	0,4 (0,1-1.4)	1,1 (0.1-28)	0.003

Discussion

AF is an arrhythmia associated with hemostatic abnormalities and an increased risk of thromboembolic events [12,13]. Thromboembolism recurrence rates and the frequency of cardiovascular events are increasing due to AF [3]. Identification of risk factors for stroke in patients with AF and initiation of OAC treatment to patients at high-risk have a privileged position. CHA_2DS_2-VASc scoring is used to identify stroke risk factors. One-year event rate of patients with a CHA_2DS_2 score of 0 ranges as follows: 0.84% (CHA_2DS_2-VASc score=0), 1.75% (CHA_2DS_2-VASc score=1), 2.69% (CHA_2DS_2-VASc=2), and 3.2% (CHA_2DS_2-VASc=3) [14]. In addition to risk scoring in patients with AF, some biomarkers have also been used to determine the risk of stroke. In the literature, elevated plasma BNP levels were reported in non-valvular AF patients with thromboembolism episodes [15]. In another study, plasma BNP levels in AF have been shown to increase in the acute phase of CVA and decrease within 1 month [16]. Plasma BNP levels have been suggested to be a promising effective biomarker in distinguishing high-risk AF

from low-risk AF. However, it has not been reported whether BNP is predictive before thromboembolic events in patients with atrial fibrillation [17]. High BNP levels have been shown in patients with congestive heart failure and stroke in the literature [16,18]. There are not enough studies examining the relationship between BNP and CHA_2DS_2-VASc score in the literature. In our study, we have identified significantly higher plasma BNP levels in high-risk group compared to low-risk group and a positive correlation between CHA_2DS_2-VASc score and BNP.

Plasma inflammatory markers have been reported to be associated with prognosis after ischemic stroke and cardiac events [19]. Plasma hs-CRP levels have been concluded to be a predictor of carotid atherosclerosis, stroke and CAD [20-23]. But the role of increased inflammatory markers in determining the prognosis after first ischemic stroke is not clear [21]. In the last statement made by European CRP Pooling Project, it has been concluded that there is insufficient data in the relationship between plasma hs-CRP levels in stroke patients [21]. In another study, significant association was found between $CHADS_2$ score and systemic inflammation, left atrial thrombus formation and cardiovascular events in patients with non-valvular atrial fibrillation. As a result of this study, a significant relationship was found between plasma CRP levels and $CHADS_2$ score [24]. A positive correlation was also found between CHA_2DS_2-VASc and CRP, hs-CRP levels in our study. As a result of our study similar to the above study, plasma CRP and hs-CRP levels were significantly higher in patients with a CHA_2DS_2-VASc ≥ 2 compared to those with a score <2. In our study, as patients with inflammatory and infectious diseases, collagen tissue diseases, active TB, malignancy and patients on Warfarin were excluded, CRP and hs-CRP levels were unaffected by these factors and this did not affect our study negatively.

vWF levels in patients with AF have been shown to be significantly higher compared to patients with sinus rhythm [25]. vWF levels have been identified to increase in women with AF, but no similar association was found in men [26]. Stroke and vascular events are known to occur due to endothelial dysfunction [27]. In his study, Roldan V et al. [4], have determined significantly higher vWF levels in AF patients with $CHADS_2 \geq 2$. In our study, vWF levels in patients with CHA_2DS_2-VASc score ≥ 2 were significantly higher than the low-risk group. In addition to the increased hypercoagulability in patients with AF, fibrinolytic system is impaired [28]. Plasma D-Dimer levels have been guiding in determining the risk of thromboembolism and deciding to start antithrombotic treatment in AF [28]. Elevated levels of plasma D-Dimer in patients with AF have been associated with increased thromboembolic and cardiovascular events [28]. Further, combined with clinical risk factors, plasma D-dimer levels have been concluded to be useful in risk scoring classification [18]. Prothrombotic state in AF is caused by vascular endothelial dysfunction, stasis and thrombus formation in the left atrium and low fibrinolytic functions [29]. These causes lead to thromboembolism and the embolism activates the coagulation systems, which in turn increases levels of plasma D-dimer, which is fibrin degradation product [29]. In clinical trials, warfarin use has been shown to reduce plasma D-Dimer levels [30]. Plasma D-Dimer levels in the high-risk group were also found to be higher than the low-risk group in our study. As we excluded the patients on warfarin from our study, the plasma D-dimer levels were not affected by warfarin and this increased the accuracy of the results of our study.

Conclusion

In conclusion, the relationship between CHA_2DS_2-VASc risk score and inflammation (CRP, hs-CRP) and coagulation (BNP, D-dimer, vWF) was found to be significant. In addition to CHA_2DS_2-VASc risk score, plasma CRP, hs-CRP, BNP, D-dimer, vWF levels may help in identification of risk factors for stroke and decision making for starting anticoagulation therapy in patients with AF.

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