Journal of the Neurological Sciences 324 (2013) 49–52

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Neutrophil/lymphocyte ratio is associated with thromboembolic stroke in patients with non-valvular atrial fibrillation

Gökhan Ertaş [a,*], Osman Sönmez [a], Murat Turfan [a], Şeref Kul [a], Ercan Erdoğan [a], Abdurrahman Tasal [a], Ahmet Bacaksiz [a], Mehmet Akif Vatankulu [a], Özge Altıntaş [b], Hüseyin Uyarel [a], Ömer Göktekin [a]

[a] Bezmialem Vakif University, Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[b] Bezmialem Vakif University, Faculty of Medicine, Department of Neurology, İstanbul, Turkey

ARTICLE INFO

Article history:
Received 7 August 2012
Received in revised form 24 September 2012
Accepted 27 September 2012
Available online 16 October 2012

Keywords:
Neutrophil/lymphocyte ratio
Atrial fibrillation
Thromboembolic
Stroke

ABSTRACT

Background: Neutrophil/lymphocyte ratio (NLR) has been associated with poor outcomes in patients with cardiovascular diseases. However, little is known about the role of NLR in patients with thromboembolic stroke due to atrial fibrillation (AF). We aimed to compare the NLR ratios between non-valvular AF patients with or without thromboembolic stroke.

Methods: A total of 126 non-valvular AF patients with or without stroke were included in the study; 126 consecutive patients (52 males and 74 females), mean age, 70 ± 10.2 years old. No patient had a recent history of an acute infection or an inflammatory disease. Baseline NLR was measured by dividing neutrophil count to lymphocyte count. WBC count > 12.000 cells per μL or <4.000 cells per μL and high body temperature > 38 º are excluded from the study.

Results: Mean NLR was significantly higher among persons with stroke compared to individuals without a stroke (5.6 ± 3.4 vs. 3.1 ± 2.1, p = 0.001). There were no significant differences in RDW levels between the two groups (p > 0.05). HAS-BLED and $CHADS_2$ scores were significantly higher in the stroke group.

Conclusion: Higher NLR, an emerging marker of inflammation, is associated with thromboembolic stroke in non-valvular AF patients.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases the risk of stroke and death. The prevalence of AF increases due to the ageing of the population. $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke) and CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category) scores have been developed to optimize stroke risk stratification and antithrombotic treatment. Warfarin is the first-line treatment for stroke prevention in patients with AF [1,2].

Biomarkers have been investigated for improving stroke prediction in AF beyond clinical scores. Mean platelet volume (MPV) has been reported as a predictive marker for stroke in patients with AF [3]. Also, troponin I and NT-proBNP have been showed independently related to increased risks of stroke in patients with AF [4]. However, some studies have revealed a relationship between inflammatory biomarker blood levels and thromboembolic stroke [5]. However, little is known about the role of NLR in patients with thromboembolic stroke due to non-valvular AF. The aim of this study was to determine the association between neutrophil/lymphocyte ratio (NLR) and thromboembolic stroke in patients with non-valvular AF.

2. Methods

2.1. Patient selection

We retrospectively analyzed 126 consecutive non-valvular AF patients (mean age, 70 ± 10.2 years; 52 male and 74 female) with or without thromboembolic stroke. A normal sinus rhythm group was taken in order to serve as a reference point for the comparison with AF group (24 patients, mean age, 38 ± 7 years; 14 male and 10 female) with AF. Patients were classified for stroke risk by using $CHADS_2$ score and for bleeding risk by using HAS-BLED score [6,7]. No patient had a recent history of an acute infection or an inflammatory disease. Patients with renal failure, concomitant valvular disease, cardiomyopathy, previous thromboembolism and previous cardiac surgery were excluded. Baseline characteristics of patients are presented in Table 1.

* Corresponding author at: Department of Cardiology, Bezmialem Vakif University, Faculty of Medicine, Adnan Menderes Bulvarı Vatan Caddesi, 34093 Fatih/İstanbul, Turkey. Tel.: +90 212 523 37 19, +90 212 453 17 00; fax: +90 212 533 23 26.
E-mail address: drgokhanertas@yahoo.com.tr (G. Ertaş).

0022-510X/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2012.09.032

Table 1
Baseline characteristics of patients.

	Group-1 Control Sinus rhythm n: 24	Group-2 AF (+) Stroke (−) n: 87	Group-3 AF (+) Stroke (+) n: 39	p
Age, years	38 ± 7	69 ± 11	71 ± 9.5	0.001* 0.394**
Gender (%/%—male/female)	58/42	44/56	36/63	0.183*
Diabetes mellitus n (%)	–	15 (17)	8 (20)	0.66
Hypertension n (%)	–	56 (65)	36 (94)	0.001
Coronary artery disease n (%)	–	64 (74)	22 (56)	0.056
Current smoker n (%)	–	4 (4)	4 (10)	0.29
Hyperlipidemia n (%)	–	17 (19)	26 (66)	<0.001
Systolic blood pressure (mm Hg)	120 ± 5	127 ± 9	145 ± 27	0.01**
Diastolic blood pressure (mm Hg)	80 ± 5	77 ± 11	82 ± 10	0.167**
$CHADS_2$	–	1.46 ± 0.7	3.56 ± 0.7	<0.001
HAS-BLED	–	1.35 ± 0.7	3.36 ± 1.1	<0.001
Warfarin n (%)	–	50 (58)	29(74)	0.108
Aspirin n (%)	–	50 (58)	19 (51)	0.462
Betablocker n (%)	–	52 (60)	13(33)	0.008
Clopidogrel n (%)	–	6 (7)	4(12)	0.420
Digoxin n (%)	–	20 (23)	7 (17)	0.484
ACE-I n (%)	–	35 (34)	18 (48)	0.167
LVEF (%)	58 ± 4	53 ± 11	57 ± 9	0.134*
Left atrium dimension (mm)	35 ± 4	47 ± 6	46 ± 6	0.001** 0.586*

Data are presented as numbers (%) or mean ± SD and percentage. AF: Atrial fibrillation, ACE-I: Angiotensin converting enzyme inhibitors, LVEF: Left ventricular ejection fraction.
* P-value among the groups, Anova.
** P-value between groups 2–3, Student-t.

2.2. Echocardiographic assessment

Transthoracic 2-dimensional and Doppler echocardiographic assessment was performed by Philips HD11 XE with a 2.5 MHz phased-array transducer (Philips Medical Systems, Andover, MA, USA). Measurements of the left atrium, left ventricle and right ventricle were obtained from parasternal long axis view according to standard criteria. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule in the 2- and 4-chamber apical views [8].

2.3. Blood samples

The blood samples were taken at admission. Fasting blood samples were drawn from a large antecubital vein of each patient for determination of biochemical and haemostatic parameters. The tubes with EDTA were used for automatic blood count. The blood counts were measured on a Sysmex XT-1800i Hematology Analyzer (Sysmex Corporation, Kobe, Japan). Total cholesterol, low-density lipoprotein (LDL) cholesterol, albumin, creatinine levels and sedimentation rate was measured conventional methods. Baseline NLR was measured by dividing neutrophil count to lymphocyte count. White blood cell (WBC) count > 12.000 cells per μL or <4.000 cells per μL and high body temperature > 38 º are excluded from the study.

2.4. Statistical analysis

The statistical analyses were performed using software (SPSS 15.0, SPSS Inc., Chicago, IL). Parametric values were given as mean ± standard deviation and non-parametric values were given as percentage. To compare parametric continuous variables, Student's t-test or analysis of variance was used; to compare nonparametric continuous variables, the Mann–Whitney U-test or the Kruskall–Wallis test was used. Categorical data were compared by Chi-square distribution. Forward stepwise multivariate logistic regression models were created to identify independent predictors of stroke. Two-tailed P-values of less than 0.05 were considered to indicate statistical significance.

2.5. Ethical considerations

The study was conducted in accordance with Declaration of Helsinki and approved by institutional ethics committee. All patients and controls gave informed consent prior to entry into this study.

3. Results

3.1. Sample characteristics

There were no significant differences among patients with or without stroke in terms of gender, age, coronary artery disease, diabetes mellitus, smoking. The mean age of the study population was 70 ± 10.2 years. LVEF and left atrium dimensions were similar between the 2 groups (Table 1). $CHADS_2$ and HAS-BLED scores were significantly higher in the stroke group ($p<0.001$). Warfarin usage rates were similar in AF patients with or without stroke ($p=0.108$).

3.2. The relationship between NLR and thromboembolic stroke

The patients with stroke showed significantly increased mean values for white blood cell (WBC) counts and NLR values (8.6 ± 2.8 vs. 7.8 ± 1.8, $p=0.014$; 5.6 ± 3.4 vs. 3.1 ± 2.1, $p=0.001$, respectively). There weren't any significant differences between stroke or without stroke group in RDW levels ($p>0.05$), but RDW levels in the AF group were significantly higher than in the control group ($p=0.027$). Comparisons of laboratory parameters among patients with or without stroke are shown in Table 2.

The study population was divided into tertiles based on admission NLR values. A high NLR ($n=42$) was defined as a value third tertile (>3.17), and as a low NLR ($n=84$) was defined as a value in lower two tertiles (≤3.17). Stroke rate and $CHADS_2$ scores were significantly higher in the high NLR (>3.17) group than the low (≤3.17) group. Baseline characteristics of NLR groups are presented in Table 3.

3.3. Univariable and multivariable predictors

Variables found to be statistically significant in univariate analyses were entered into multivariate logistic regression analysis. In multivariate analysis, hypertension, hyperlipidemia and NLR > 3.17 were

Table 2
Comparison of laboratory parameters among patients with or without stroke.

	Control group Sinus rhythm n: 24	AF(+) Stroke(−) n: 87	AF(+) Stroke(+) n: 39	p
Hemoglobin (gr/dL)	14 ± 1.7	13 ± 1.4	13 ± 1.6	0.037
Platelets (10^3/mm3)	258 ± 54	232 ± 55	240 ± 82	0.259
White blood cell count ($\times 10^9$/L)	7.0 ± 1.4	7.8 ± 1.8	8.6 ± 2.8	0.014
NLR	2.05 ± 0.9	3.1 ± 2.1	5.6 ± 3.4	0.001
RDW	13.2 ± 0.9	14.3 ± 1.8	14.1 ± 1.7	0.027

Results are expressed as mean ± SD. AF: Atrial fibrillation, NLR: Neutrophil/lymphocyte ratio, RDW: Red blood cell distribution width.

Table 3
Baseline characteristics of NLR groups.

	NLR ≤ 3.17 n = 84	NLR > 3.17 N = 42	p
Age, years	59.1 ± 17	72.7 ± 9	<0.001
Hypertension	44 (53)	32 (78)	0.006
Diabetes mellitus	11 (13)	8 (19)	0.379
Hyperlipidemia	22 (27)	15 (35)	0.3
Coronary artery disease	21 (25)	12 (28)	0.6
Stroke	20 (23)	19 (45)	0.014
$CHADS_2$	1.5 ± 1.3	2.4 ± 1.3	0.001
Warfarin	43 (53)	21 (50)	0.7
Aspirin	30 (36)	25 (61)	0.008
LVEF (%)	56.7 ± 9.6	53.3 ± 11.4	0.153
Left atrium dimension (mm)	46.1 ± 5.6	46.6 ± 6.4	0.76

Results are expressed as mean ± SD and percentage. LVEF: Left ventricular ejection fraction, NLR: Neutrophil/lymphocyte ratio.

independent correlates of the presence of stroke (Table 4). Using stepwise multivariate Cox proportional hazards regression analyses, NLR was a significant independent predictor of stroke (hazard ratio 3.0, %95 CI 1.0–8.5, p = 0.03).

4. Discussion

WBC count and its subtypes have been found as markers of inflammation in cardiovascular disease [9]. Also, NLR has been shown as an indicator of systemic inflammation [10]. In an acute setting, lymphopenia is a common finding during a stress response second to increased levels of corticosteroids [11]. Lymphopenia is observed in inflammatory states due to increased lymphocytes apoptosis [12]. Lymphopenia has been found to be related with mortality after ST-segment elevation myocardial infarction [13]. In addition, the NLR has been associated with long-term mortality in patients with ST-segment elevation myocardial infarction and acute decompensated heart failure [14,15]. There is an established relation between NLR and poor outcomes in patients with cardiovascular diseases.

In another report, patients with cardioembolic strokes have showed significantly higher immuno-inflammatory activation compared to other subtypes of ischemic stroke [5]. Inflammation plays a key role at multiple stages in AF. Inflammation is an important factor related to the initiation and maintenance of AF [16–18]. The abnormal inflammatory state may cause a prothrombotic state in AF which can lead to a thromboembolism [19]. With the growing understanding of the role of inflammation in the AF, studies have focused on C-reactive protein and other inflammatory markers for the evaluation of risk of stroke in patients with AF [20]. Lip et al. have revealed that CRP was positively correlated to stroke risk in patients with AF [20]. Pinto et al. investigated the occurrence of stroke in patients with chronic non-valvular AF, evaluating the relationship between plasma levels of inflammatory markers. After 3 year follow up, baseline plasma levels of interleukin-6, TNF-alpha (tumor necrosis factor-alpha), vWF (von Willebrand Factor) were predictors of new-onset ischaemic stroke in patients with chronic non-valvuler AF [21]. Also, other cardiac biomarkers such as troponin I and NT-proBNP have predicted stroke risk in patients with AF [4].

Table 4
Independent predictors of stroke in multivariate logistic regression analysis.

Variables	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age, years	–	0.001	–	0.2
Coronary artery disease	3.4 (1.4–7.8)	0.004	–	0.4
Hypertension	20.7 (4.7–91.5)	<0.001	5.9 (1,2–29,5)	0.02
Hyperlipidemia	12.5 (5.0–30.8)	<0.001	7.2 (2.5–20.2)	<0.001
NLR > 3.17	1.3 (1.0–1.5)	0.003	3.0 (1.0–8.5)	0.03
Warfarin	0.2 (0.1–0.5)	0.001	3.3 (1.1–9.7)	0.03
Statin	3.8 (1.5–9.8)	0.005	–	0.1

NLR: Neutrophil/lymphocyte ratio.

Little is known, however, about the association of NLR levels with thromboembolic stroke in patients with non-valvular AF. We demonstrated that the NLR is an independent predictor of thromboembolic stroke in patients with non-valvular AF. To the best our knowledge, this is the first report showing that NLR is associated with thromboembolic stroke in patients with non-valvular AF.

Inflammatory markers might improve stroke prediction in AF beyond clinical scores such as $CHADS_2$ and CHA_2DS_2-VASc. In the present study, $CHADS_2$ scores were also significantly higher in the high NLR group. In the light of our data, anticoagulation may be needed in patients with high NLR levels. It is not well known at present whether reductions of inflammatory markers would have a beneficial effect on the clinical incidence of thromboembolic stroke in patients with AF. It is reasonable that the prevention of thromboembolism in patients with high NLR levels might be improved by the use of antiinflammatory agents.

4.1. Limitations of the study

Number of patients who were included in the study was a limitation of our study. Our analysis is cross-sectional observational in nature and prospective data regarding the NLR and thromboembolic stroke are awaited. And also we did not look leukocyte and lymphocyte subtypes.

5. Conclusion

In summary, NLR is an inexpensive inflammatory marker that is associated with thromboembolic stroke in patients with non-valvular AF. We hope this study will stimulate a prospective investigation about the relationship between NLR and thromboembolic stroke in AF.

Conflict of interest

None declared.

References

[1] Pieri A, Lopes TO, Gabbai AA. Stratification with CHA_2DS_2-VASc score is better than $CHADS_2$ score in reducing ischemic stroke risk in patients with atrial fibrillation. Int J Stroke 2011;6:466.
[2] Mason PK, Lake DE, DiMarco JP, Ferguson JD, Mangrum JM, Bilchick K, et al. Impact of the CHA_2DS_2-VASc score on anticoagulation recommendations for atrial fibrillation. Am J Med 2012;125:603.
[3] Ha SI, Choi DH, Ki YJ, Yang JS, Park G, Chung JW, et al. Stroke prediction using mean platelet volume in patients with atrial fibrillation. Platelets 2011;22: 408-14.
[4] Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation 2012;125:1605-16.
[5] Licata G, Tuttolomondo A, Di Raimondo D, Corrao S, Di Sciacca R, Pinto A. Immuno-inflammatory activation in acute cardio-embolic strokes in comparison with other subtypes of ischaemic stroke. Thromb Haemost 2009;101:929-37.
[6] Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack ($CHADS_2$) risk stratification scheme. Am Heart J 2008;156:57-64.
[7] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1 year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100.
[8] Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358-67.
[9] Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Intermountain Heart Collaborative Study Group. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638-43.
[10] Zahorec R. Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;1:5–14.

[11] Onsrud M, Thorsby E. Influence of in vivo hydrocortisone on some human blood lymphocyte subpopulations. Effect on natural killer cell activity. Scand J Immunol 1981;13:573-9.
[12] Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138-50.
[13] Pellizzon GG, Dixon SR, Gregg W, Cox DA, Mattos L, Boura JA, et al. Stent PAMI Investigators. Relation of admission white blood cell count to long-term outcomes after primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 2003;91:729-31.
[14] Núñez J, Núñez E, Bodí V, Sanchis J, Miñana G, Mainar L, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol 2008;101:747-52.
[15] Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011;107:433-8.
[16] Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108: 3006-10.
[17] Aronson D, Boulos M, Suleiman A, Bidoosi S, Agmon Y, Kapeliovich M, et al. Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. Am J Cardiol 2007;100:753-7.
[18] Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias. Inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886-91.
[19] Marin F, Corral J, Roldan V, Gonzalez-Conejero R, del Rey ML, Sogorb F, et al. Factor XIII Val34Leu polymorphism modulates the prothrombotic and inflammatory state associated with atrial fibrillation. J Mol Cell Cardiol 2004;37:699-704.
[20] Lip GYH, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation relationship to stroke risk factors, stroke risk stratification schema, and prognosis. Stroke 2007;38:1229-37.
[21] Pinto A, Tuttolomondo A, Casuccio A, Di Raimondo D, Di Sciacca R, Arnao V, et al. Immuno-inflammatory predictors of stroke at follow-up in patients with chronic non-valvular atrial fibrillation (NVAF). Clin Sci (Lond) 2009;116:781-9.