Can neutrophil/lymphocyte ratio predict recurrence of non-valvular atrial fibrillation after cardioversion?

Nötrofil/lenfosit oranı kapak hastalığının eşlik etmediği atriyal fibrilasyonda elektriki kardiyoversiyon sonrası nüksü öngördürebilir mi?

Alpay Arıbaş, Hakan Akıllı, Enes Elvin Gül, Mehmet Kayrak, Kenan Demir[1], Çetin Duman[2], Hajrudin Alibasiç, Mehmet Yazıcı, Kurtuluş Özdemir, Hasan Gök

Department of Cardiology, Faculty of Meram Medicine, Necmettin Erbakan University, Konya-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Selçuk University, Konya-*Turkey*
[2]Clinic of Cardiology, Akşehir State Hospital, Konya-*Turkey*

Abstract

Objective: High neutrophil/lymphocyte ratio (NLR) has been associated with post-operative AF development in patients who underwent cardiac surgery. In this study, effectiveness of NLR for prediction of recurrence after electrical cardioversion (CV) in non-valvular AF was investigated.
Methods: A total of 149 patients who underwent a successful CV were included in this prospective cohort study. Baseline complete blood cell count, routine biochemical tests, high sensitive C-reactive protein (hs-CRP), and echocardiographic measurements were examined. After CV, patients were monitored over six months for recurrence. Baseline characteristics of recurrence group were compared with sinus rhythm group by using Student`s t -test. Logistic regression analysis was used to determine predictors of recurrence.
Results: Recurrence occurred in a total of 46 patients (30.9%). Median AF duration [16 (IQR:14.25) vs. 12 (IQR:11) months, p=0.01], baseline hs-CRP [9.80 (IQR: 8.50) mg/dL vs. 4.28 (IQR: 5.65) mg/dL, p=0.002] and left atrium (LA) diameter (4.5±0.4 cm, 4.3±0.5 cm, p=0.023) were significantly higher in the recurrence group than sinus rhythm group. Median NLR was comparable in recurrence and sinus groups [2.38 (IQR: 2.09) vs. 2.23, (IQR: 1.23) p=0.96, respectively]. There was a weak correlation between NLR and hs-CRP (r=0.22, p=0.05) and age (r=0.24, p=0.02). In multiple logistic regression analysis, hs-CRP [OR: 1.34 (1.09-1.65 95% CI) p=0.006], LA diameter [OR: 11.92 (1.84-77.07 95% CI) p=0.01], spontaneous echo contrast positivity, [OR: 5.40 (1.04-12.02 95% CI) p=0.045] and systolic blood pressure [OR: 1.05 (1.01-1.10 95% CI) p=0.03] were independent predictors of AF recurrence.
Conclusion: NLR failed to predict AF recurrence after a successful electrical CV, but hs-CRP remained an inflammatory marker of AF recurrence. *(Anadolu Kardiyol Derg 2013; 13: 123-30)*
Key words: Atrial fibrillation, electric countershock, inflammation, recurrence, neutrophils- lymphocytes, logistic regression analysis

ÖZET

Amaç: Yüksek nötrofil/lenfosit oranının (NLO) koroner arter baypas cerrahisi sonrası atriyal fibrilasyon (AF) gelişmesiyle ilişkili olduğu gösterilmiştir. Bu çalışmada NLO'nın kapak hastalığının eşlik etmediği AF'de elektriki kardiyoversiyon (KV) sonrası nüksü öngördürmede etkinliği araştırıldı.
Yöntemler: Bu prospektif kohort çalışmasına, elektriki KV sonrası başarılı olunan toplam 149 hasta alındı. Tüm hastaların KV öncesi; kişisel bilgileri kaydedildi, tam kan sayımı, alışılagelen biyokimyasal tetkikleri ve yüksek duyarlılıklı C-reaktif protein (hs-CRP) çalışıldı. İşlem öncesi ekokardiyografik ölçümleri kaydedildi. KV sonrası hastalar rekürrens açısından altı ay takip edildi. Nüks gelişen grubun bazal karakteristikleri sinüs grubu ile Student t- testi kullanılarak karşılaştırıldı. Rekürrensin bağımsız öngördürücüleri lojistik regresyon analizi ile araştırıldı.
Bulgular: Kırk altı hastada (%30.9) nüks izlendi. Nüks grubunda AF süresi [ortanca: 16 (çeyrekler arası aralık (ÇAA): 14.25]'e karşın, ortanca: 12 (ÇAA: 11) ay, p=0.01) ve sol atriyum (SA) çapı (4.5±0.4 cm'e karşın, 4.3±0.5 cm, p=0.023) belirgin uzun bulundu. Nüks gurubunda, sinus ritmine oranla başlangıç hs-CRP değerleri belirgin yüksek (ortanca: 9.80'e (ÇAA: 8.50) karşın ortanca: 4.28 (ÇAA: 5.65) mg/dL, p=0.002) iken, NLO her iki grupta benzerdi. [rekürrens grubunda ortanca: 2.38 (ÇAA: 2.09), sinüs grubunda ortanca:2.23 (ÇAA: 1.23), p=0.96]. NLO ile hs-CRP seviyeleri (r=0.22, p=0.05) ve yaş (r=0.24, p=0.02) arasında zayıf bir pozitif ilişki mevcuttu. Çoklu lojistik regresyon analizinde hs-CRP [OO: 1.34 (1.09-1.65

Address for Correspondence/Yazışma Adresi: Dr. Alpay Arıbaş, Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Meram, Konya-*Türkiye* Phone: +90 332 223 78 50 Fax:+90 332 323 94 43 E-mail: draribas@hotmail.com
Accepted Date/Kabul Tarihi: 02.10.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 07.12.2012
©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.
©Copyright 2013 by AVES Yayıncılık Ltd. - Available on-line at www.anakarder.com
doi:10.5152/akd.2013.036

%95 GA)] p=0.006) SA çapı [OO: 11.92 (1.84-77.07 %95 GA) p=0.01], spontan eko kontrast varlığı [OO: 5.40 (1.04-12.02 %95 GA) p=0.045] ve sistolik kan basıncı [OO: 1.05 (1.01-1.10 %95 GA) p=0.03] nüksün bağımsız öngördürücüleri olarak izlendi.
Sonuç: NLO başarılı kardiyoversiyon sonrası AF nüksünü öngördürmede etkisiz bulunmuştur. Hs-CRP başarılı kardiyoversiyon sonrası nüksü öngördürmede etkin olarak kullanılabilir. *(Anadolu Kardiyol Derg 2013; 13: 123-30)*
Anahtar kelimeler: Atriyal fibrilasyon, elektriki şok, enflamasyon, nüks, nötrofil-lenfosit, lojistik regresyon analizi

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice. One-third of arrhythmia-related hospitalizations and stroke after age 60 are due to AF. AF both reduces quality of life and leads to a relative increase in risk of mortality (1, 2). Increased AF frequency in pericarditis, myocarditis and after cardiac surgery suggests that inflammation may play a role in AF development (3, 4). In studies investigating the AF-inflammation relationship using serum markers, inflammatory markers like C-reactive protein (CRP), interleukin 6 (IL-6), high-sensitive CRP (hs-CRP), a relationship between inflammatory markers and AF development and continuity has been proposed (5-7). Neutrophil/lymphocyte ratio (NLR), which can be derived from the white blood cell (WBC) count, is a novel marker of prognosis in patients with cardiovascular disease (8, 9). Whereas high neutrophil counts reflect inflammation, low lymphocyte counts reflect poor general health and physiologic stress (10). NLR combines these two independent markers of inflammation (8). In several studies, it has been shown that NLR is an indicator of systemic inflammation (11). In a recent study, increased NLR has been shown to be related to AF development after cardiac surgery (10).

However, there is no knowledge on predictive value of NLR after AF cardioversion.

In the present study was aimed to investigate the relationship between NLR and AF recurrence after a successful cardioversion (CV).

Methods

Study design and sample size

The study design is prospective cohort study. Power analysis was performed using the Minitab 16 packet program. Sample volume was calculated as 150 to determine the difference of one unit NLR with 80% power. A total of 156 patients whose CV was successful were included in the study, accounting for possible losses in the follow-up.

Patient selection

A total of 300 persistent AF patients, who remain symptomatic in European Heart Rhythm Association (EHRA) classes II-III despite medical therapy, were prospectively screened between 01.01.2009 and 01.01.2011. A total of 156 patients whose CV was successful were included in the study. Seven patients were lost to follow up over a six month period. Consequently, 149 patients (80 female and 69 male) were monitored for six months. A flow chart of the study is shown in Figure 1. The study was approved by a local ethics committee. Written informed consent was obtained from all patients participating in the study.

Exclusion criteria were as follows: severe valvular stenosis or insufficiency (> grade 2), congestive heart failure and severe left ventricle dysfunction, a history of acute coronary syndrome (ACS) in previous six months, presence of hyperthyroidism, hypothyroidism, chronic obstructive pulmonary disease (COPD), malignity, acute infectious disease and AF <7 days.

Demographics

Resting systolic and diastolic blood pressures (BP) of the patients were measured from both arms within a 5 min interval using an aneroid sphygmomanometer (Erkameter, Germany) before CV. Systolic and diastolic BP were determined by the mean of two consecutive measurements. Korotkoff I sound for systolic BP and Korotkoff V sound for diastolic BP were taken as reference values. Patients whose BP ≥140/90 mmHg and who were currently using antihypertensive drugs were considered hypertensive (12). Apical heart beat rates were recorded. Weight and height of all patients were measured and body mass index (BMI) (kg/m^2) was calculated using weight/height^2 formula. The patients questioned on duration of AF, history of diabetes mellitus (DM), and coronary artery disease (CAD). All drugs used by the patients were recorded.

Study protocol

Initially 300 persistent AF patients, symptomatic in EHRA classes II-III despite medical therapy, were screened, questioned for medical history and functional capacity, and demographics, and transthoracic echocardiography (TTE) was performed in the outpatient clinic at first visit. The patients who did not fall within the exclusion criteria and who accepted the informed consent were scheduled for transesophageal echocardiography (TEE). Following 12 hours fasting, a blood sample was obtained for complete blood cell (CBC) count, routine biochemical tests, and hs-CRP. After taking a blood sample, TEE was performed. Thrombus was seen in seven patients in left atrial appendix (LAA) and these patients were excluded from the study. The rest of 161 eligible patients were admitted to the intensive care unit of the cardiology department and CV was performed immediately after TEE. Direct current-CV (DC-CV) was performed using biphasic direct current (Nihon Kohden Corporation TEC-5521K Tokyo, Japan) synchronized with R waves on electrocardiography (ECG) under sedation achieved with intravenous (IV) propofol (2 mg/kg). Pedals were placed in antero-lateral (right parasternal and left apical) position. CV was started with 100 biphasic joule (J) and gradually elevated to 150 and 200 J if not achieved with 100 J. In unsuccessful cases, elec-

trical shock was applied a maximum 4 times in total, with the last one applied with 200 J in antero-posterior position. CV was considered successful in patients in whom sinus rhythm was kept for ≥15 min following CV (13). 300 mg IV amiodarone was administered prior to CV according to antiarrhythmic drug protocol. 200 mg/day amiodarone was given to all patients for 1 month following CV. All patients received warfarin so as to maintain International Normalized Ratio (INR) at >2 for 1 month following CV. Warfarin was continued during follow-up in patients whose CHA_2DS_2-VASc score was ≥2 and was ceased at the end of one month in the rest of the patients. Patients were divided into two groups depending on the presence or absence of recurrence, as recurrence of AF and maintenance of sinus rhythm groups.

Follow- up period

Patients were examined for a total of 4 times at weeks 2 and 4 and at months 3 and 6 unless they had complaint of palpitation. Patients who had a complaint of palpitation were evaluated separately with 12 derivation ECG and 3 days of Holter electrocardiographic (ECG) monitoring at the time of palpitation besides periodical controls. Recurrence was defined as episodes of >30 sec. paroxysmal AF (PAF) on 12- derivation ECG at 6 months follow up or 3 days of Holter monitoring in patients who had a complaint of palpitation (13). No patients developed embolic or hemorrhagic complication during 6 months of follow-up. Seven patients were lost in the follow- up, so 149 patients completed the six months follow up period.

Echocardiography

In all patients, echocardiography was performed using a Philips Envisor C HD echocardiography device (Philips Medical system, Andover, Massachusetts, USA). A 2-4 MHz (Philips S4-2 broadband sector array) transducer was used for TTE and a 4.8-6 MHz (S6-2 MPT TEE) transducer was used for TEE. Patients were examined in left decubitis position. Assessments were done according to American Echocardiography Association criteria, obtaining parasternal long axis, short axis, apical four chamber and two chamber images (14). Ejection fraction (EF) was estimated by the modified Simpson's method by measuring left ventricle end-diastolic volumes and end-systolic volumes in apical four-chamber images. Left atrium (LA) diameter was measured using parasternal long axis images. All patients underwent TEE with local anesthesia and mild sedation following fasting for 12 hours. The presence of thrombus or spontaneous echo contrast (SEC) in the LA and LAA were evaluated with TEE. SEC was defined as a pattern of slowly swirling intracavity echocardiographic densities imaged with gain settings adjusted to distinguish background noise (11).

Blood sample analyses

CBC count including WBC, neutrophil and lymphocyte counts were done using an automatized CBC count device (Abott Cell Dyn, Illinois USA). NLR was calculated using data obtained from the CBC count. Hs-CRP measurement was done using an automatized analyzer (Beckman Coulter, USA) with Diasys Diagnostic System kits (DiaSys Diagnostic Systems GmbH, Holzheim, Germany), using immuno-turbidimetric measurement.

Statistical analyses

All statistical assessments were done using SPSS 15 package program (SPSS Inc, Chicago, IL, USA). Normal distributed data were given as mean±SD, data with non-normal distributions were expressed as median (IQR), and dichotomous data were given as percent. Significance level of the difference between two groups was analyzed using parametric t-test for normal distributing variables and with the non-parametric Mann-Whitney U test used for non-normally distributed variables. Differences between dichotomous variables were evaluated using the chi-square test. Linear association between parametric variables was evaluated with Pearson's correlation test. Logistic regression analysis was done using the backward elimination method to determine predictors of recurrence development. AF duration, DM, systolic and diastolic BP, hypertension, SEC state (+ status reference), BMI, gender (female reference), LA diameter, and NLR were entered into a regression model as independent predictors of AF recurrence. After six step elimination, only four variables remained in the model as predictors of AF recurrence. Level of statistical significance was accepted as $p<0.05$.

Results

Baseline demographics and characteristics

Recurrence developed in a total of 46 patients (30.9%). Patients were divided into groups according to recurrence. There was no significant difference in drugs used by the patients in each group. Baseline clinical characteristics, CBC count hs-CRP values before CV and echocardiographic parameters of the patients with or without recurrence are seen in Table 1. There was no a difference between recurrence and sinus rhythm groups in terms of age. Duration of AF was found to be significantly longer in the recurrence group compared to the sinus rhythm group [median: 16 (IQR: 14.25) vs. median: 12 (IQR: 11) months, p=0.01]. Of assessed echocardiographic parameters, only LA diameter was different between the two groups and LA was enlarged in the recurrence group (4.5±0.4 cm, 4.3±0.5 cm, p=0.02). While initial hs-CRP values were significantly higher in patients in the recurrence group in comparison to the sinus rhythm group [median: 9.80 (IQR: 8.50) mg/dL vs median: 4.28 (IQR: 5.65) mg/dL, p=0.002], When patients were divided into two groups, with (n=66) and without (n=83) SEC, no significant difference was detected between the two groups in terms of baseline clinical characteristics, CBC count, hs-CRP values before CV, and echocardiographic parameters.

NLR and related findings

Neutrophil/lymphocyte ratio was similar in both groups [median: 2.38 (IQR: 2.09) in recurrence group and median: 2.23

Table 1. Baseline clinical characteristics of patient, whole blood count, and hs-CRP values before CV and echocardiographic parameters

Variables	Sinus rhythm n=103 (69%)	AF recurrence n=46 (31%)	*p
Age, years	59±10	61±10	0.46
BMI, kg/m^2	28±4	29±4	0.40
SBP, mmHg	121±20	131±21	0.01
DBP, mmHg	75±11	80±13	0.02
Heart rate, bpm	102±40	103±28	0.85
CAD, n (%)	18 (17)	13 (28)	0.15
Hypertension, n (%)	62 (60)	30 (65)	0.56
Diabetes Mellitus, n (%)	18 (17)	19 (41)	0.002
Smoking, n (%)	17 (16)	10 (21)	0.55
AF duration, month	12 (11)	16 (14.25)	0.01
Energy, joule	100 (87.3)	100 (125)	0.69
EF, %	54±10	56±8	0.22
LA Diameter, cm	4.3±0.5	4.5±0.4	0.02
LVDD, cm	4.95±0.6	4.77±0.5	0.10
LVSD, cm	3.24±0.6	3.05±0.6	0.13
Creatinine, mg/dL	1.0±0.4	0.9±0.3	0.33
Potassium, mEq/L	4.38±0.6	4.52±0.7	0.35
Total cholesterol, mg/dL	176±35	167±42	0.22
LDL - cholesterol, mg/dL	109±29	111.±31	0.75
HDL - cholesterol, mg/dL	40±12.8	38±8	0.42
Triglyceride, mg/dL	120 (100)	106.5 (98)	0.50
WBC, 10^3/µl	7.6±2	7.4±2	0.71
Neutrophil, 10^3/µl	5.0±2	5.1±2	0.98
Lymphocyte, 10^3/µl	2.0±0.7	2.1±0.9	0.92
NLR	2.23 (1.23)	2.38 (2.09)	0.96
hs-CRP, mg/L	4.28 (5.65)	9.80 (8.50)	0.002

Data are presented as median (interquartile range), mean±standard deviation or number (percentage).
*Student t- test for independent samples, Mann-Whitney U test and Chi-square test
AF - atrial fibrillation, BMI - body mass index, CAD - coronary artery disease, DBP - diastolic blood pressure, EF - ejection fraction, HDL - high-density lipoprotein, hs-CRP - high sensitivity C-reactive protein, LA - left atrium, LDL - low-density lipoprotein, LVDD - left ventricular diastolic diameter, LVSD - left ventricular systolic diameter, NLR - neutrophil/lymphocyte ratio, SBP - systolic blood pressure, WBC - white blood cell

(IQR: 1.23) in sinus group, p=0.96] (Fig. 2). Although no correlation was seen between NLR and echocardiographic parameters, there was a weak positive correlation between hs-CRP levels and NLR (r=0.22, p=0.05) (Fig. 3). Similarly, NLR was weakly correlated with age (r=0.24, p=0.02). The other laboratory findings were comparable between the two groups.

Predictors of recurrence

Hs-CRP [OR1.34 (1.09-1.65 95%CI) p=0.006], LA diameter [OR11.92 (1.84-77.07 95% CI) p=0.01], SEC positivity [OR5.40 (1.04-12.02 95% CI) p=0.045], and systolic blood pressure [OR1.05 (1.01-1.10 95% CI) p=0.03] were found to be predictors of recurrence

Table 2. Stepwise logistic regression results for predictors of AF recurrence

	B	Odds (B)	OR 95% CI	p
1. Step				
AF Duration, month	0.03	1.03	0.96-1.10	0.48
hs-CRP, mg/L	0.32	1.38	1.07-1.79	0.01
Diabetes mellitus	1.79	5.97	0.43-83.62	0.18
BMI, kg/m^2	-0.13	0.88	0.65-1.19	0.42
Sex	0.16	1.18	0.21-6.66	0.85
LA, cm	2.80	16.47	1.94-139.94	0.01
NLR	-0.02	0.98	0.49-1.99	0.96
SEC-Positivity	2.43	11.41	1.37-95.03	0.02
SBP, mmHg	0.04	1.04	0.99-1.09	0.09
DBP, mmHg	0.09	1.10	0.95-1.23	0.12
6. Step				
hs-CRP, mg/L	0.29	1.34	1.09-1.65	0.006
LA, cm	2.48	11.92	1.84-77.07	0.01
SEC-Positivity	1.69	5.40	1.04-12.02	0.045
SBP, mmHg	0.05	1.05	1.01-1.10	0.03

AF - atrial fibrillation, BMI - body mass index, hs - CRP-high sensitivity C-reactive protein, LA - left atrium, NLR - neutrophil/lymphocyte ratio, SBP - systolic blood pressure, SEC - spontaneous echo contrast

in multiple logistic regression analysis (Table 2). While presence of DM [OR3.3 (1.5-7.2 95% CI) p=0.003] and duration of AF [OR1.05 (1.01-1.10 95% CI) p=0.01] were predictors of recurrence in univariate analysis, these were not found to be independent predictors in multiple logistic regression analysis (Table 2).

Discussion

The present study did not detect a relationship between NLR and AF recurrence after successful DC-CV. We found that hs-CRP, LA diameter, SEC positivity, and systolic BP were independent predictors of recurrence.

After cardiac surgery the presence of a relationship between AF development and interleukin 8 (IL-8), IL-6 and increased WBC count has been shown (15-17). In a very recent study, Rienstra et al. (18) examined the 936 participants in the Framingham Heart Study original cohort and found that an increased WBC count was associated with AF incident during 5 years of follow-up. In various studies assessing success rate of pharmacologic or DC-CV and presence of sinus rhythm, elevation of inflammation markers like IL-6, IL-2, hs-CRP has been shown have a negative effect (19-22). In the study of Çelebi et al. (23), hs-CRP elevation was demonstrated to be related to AF recurrence in 12 months follow up. Consistent with current literature, the present study detected an independent relationship between hs-CRP and AF recurrence, and supported significant correlation of AF and inflammation.

Neutrophil/lymphocyte ratio has been gaining attention as a significant indicator of inflammation in recent years. NLR eleva-

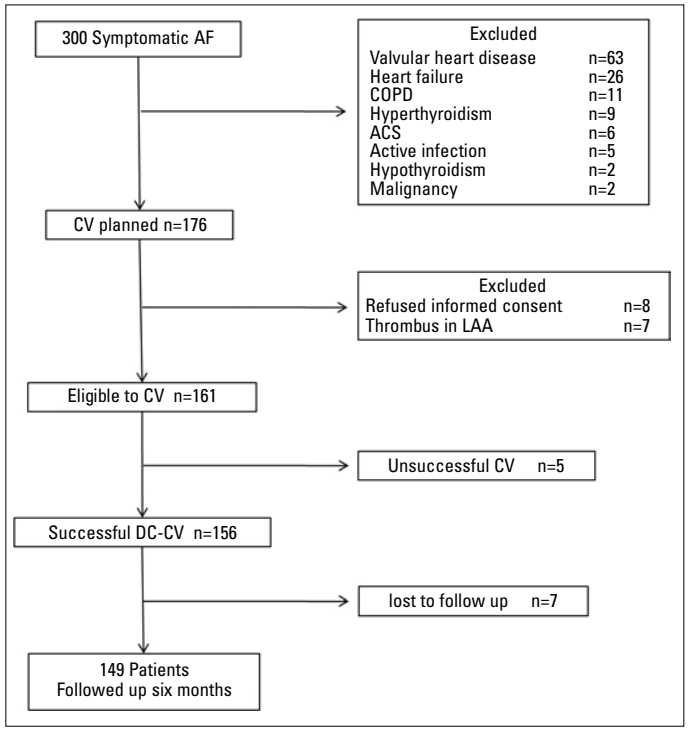

Figure 1. Flow chart of the study

ACS - acute coronary syndrome, AF - atrial fibrillation, CV - cardioversion, COPD - chronic obstructive pulmonary disease, DC - direct current, LAA - left atrial appendage

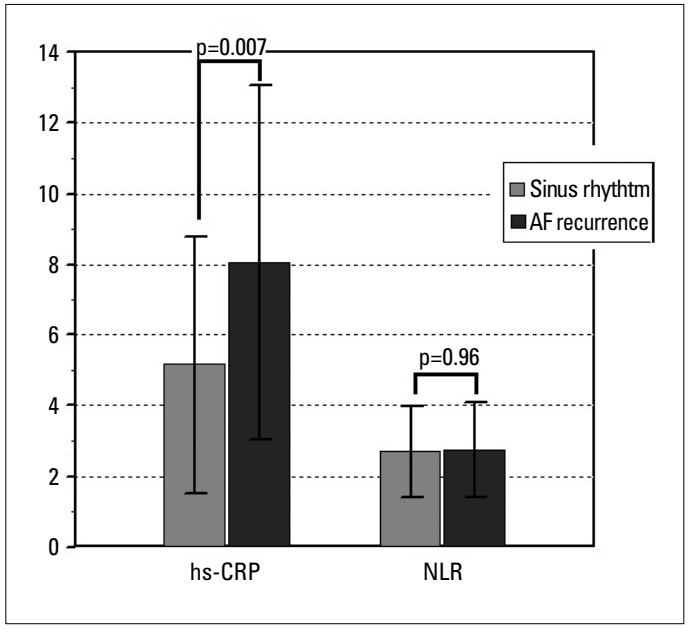

Figure 2. A comparison of baseline Hs-CRP and NLR between recurrence and sinus rhythm groups. Error bars show two standard deviation of mean values

AF - atrial fibrillation, hs - CRP-high -sensitivity C-reactive protein, NLR - neutrophil/lymphocyte ratio

tion has been shown to indicate the presence of inflammation in various diseases and poor prognosis (24, 25). NLR elevation is also known to indicate poor prognosis in ACS and stable CAD (8, 9, 26). In a recent retrospective study, the relationship of ventricular arrhythmias developing during percutaneous coronary

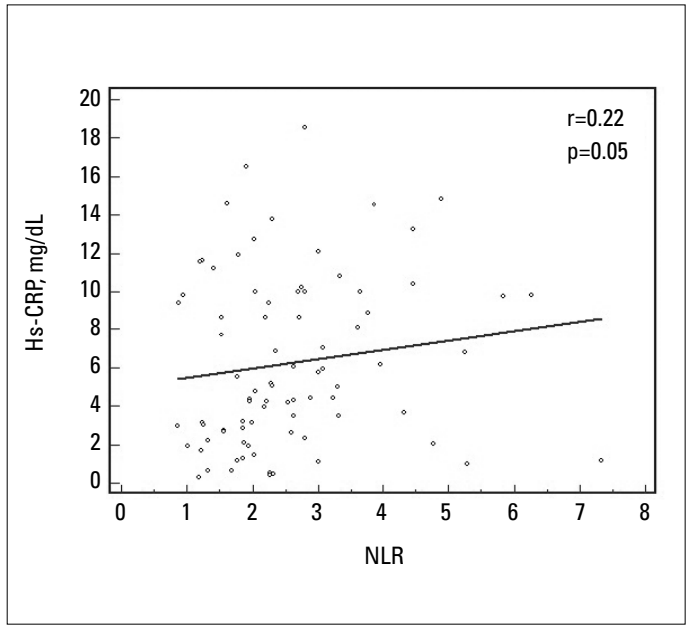

Figure 3. The linear association between hs-CRP and NLR

hs - CRP - high sensitivity C-reactive protein, NLR - neutrophil/lymphocyte ratio

interventions (PCI) to inflammatory markers like WBC count and NLR was shown (27). In this study, Chatterjee et al. (27) compared 70 patients who developed ventricular arrhythmia during the procedure out of 30.798 patients who underwent PCI within 10 years and detected significantly higher WBC count (mean 14.344 vs. 6.852; p=0.0004), neutrophil count (mean 75.79% vs. 58.06%; p<0.0001) and NLR (mean 3.79 vs. 1.56; p<0.0001) in the arrhythmia group in comparison to a control group. Chatterjee et al. (27) discussed that inflammation led to increased oxidative stress and attenuation of cell survival pathways. This consecutively caused faster apoptosis and myocardial necrosis creating a 'substrate'/scar tissue to predispose to ventricular tachyarrhythmias.

In another recent study, Gibson et al. (10) investigated the relationship between AF development after coronary artery by-pass surgery and NLR. In this study, CBC count and hs-CRP measurements were done before surgery and on the second postoperative day in 275 patients who would undergo elective coronary artery by-pass surgery. While it was shown that both preoperative and postoperative elevations in NLR were related to AF development after surgery, no relationship could be detected between AF development and other WBC parameters or CRP values. The mean NLR was determined to 3.0 vs. 2.4 (p=0.001) in the pre-operative assessment and 9.2 vs. 7.2 (p<0.001) on the postoperative second day assessment in the groups in which AF developed and did not develop, respectively. A preoperative NLR value of 2.63 had 63% sensitivity and 68% specificity for prediction of postoperative AF development. AF development risk increased two-fold in patients whose NLR values were above 2.63 (OR 2.23, 95% CI 1.36 to 3.67; p=0.002). Similarly, in patients whose preoperative NLR value was above 3.46, AF development risk increased four-fold compared to the

patients whose NLR <2.01 (OR 4.04, 95% CI 1.93 to 8.45, p<0.001). The complex nature of the inflammatory response after cardiac surgery and its relation to postoperative AF continues to be investigated (10). Both systemic and local inflammation may foster oxidative injury through the release of reactive oxygen species (ROS). ROS can induce electrical myocardial remodeling, characterized by a diminished effective refractory period to action potential, thus precipitating postoperative AF (28). High preoperative neutrophil count" may reflect subclinical inflammation. Lymphopenia is an indicator of physiologic stress and poor general health status. NLR yields information on both the inflammatory status and the stress response. This may explain the superiority of the NLR in predicting incidence of postoperative AF compared to indexes of inflammation alone used in the study conducted by Gibson et al. (10).

In both studies mentioned above, NLR values were much higher in patients in whom arrhythmic events have developed than among patients in our study. The cut-off value of NLR was 3.46 to predict post-operative AF in the study by Gibson et al. (10) and was 3.79 for development of ventricular arrhythmias in the study Chatterjee et al. (27) So, NLR values of both the recurrence group and the sinus rhythm group in our study (median NLR 2.38/2.23) were lower than NLR values of the above mentioned studies from the current literature. The lower NLR values may be related to the failure to predict of recurrence of AF in our study.

We consider NLR insufficient to indicate AF recurrence, as inflammation is of lower grade in persistent AF patients in our study compared to the aforementioned studies. While neutrophil count rapidly increases in conditions with heightened inflammation, lymphocyte count is also reduced and thus NLR increases significantly.

Increased NLR in ACS was found to be an independent predictor of in-hospital mortality and morbidity in prospective randomized controls (29, 30).

In the study by Kaya et al. (11), a relationship was found between a prothrombotic condition, SEC development and increased hs-CRP and NLR in patients with mitral stenosis. While hs-CRP was found to be 10.6±6.3 vs. 3.9± 2.2 (p=0.024) in SEC positive and negative groups, NLR values were found to be 4.5±1.8 vs. 3.0±1.8 (p=0.003). In this study, a NLR value above 3.1 mg/dL was shown to have 80 % sensitivity and 72% specificity for prediction of SEC in patients with mitral stenosis. In our study, a statistically significant difference was not detected between SEC positive and negative groups in terms of hs-CRP and NLR. Possible reasons for this may be that the degree of inflammation and SEC is greater in patients with mitral stenosis in comparison to non-valvular AF patients. In fact mean NLR values for the SEC positive group in the study by Kaya et al. (11) was 4.5 mg/dL while it was 2.38 mg/dL for the AF recurrence group in our study. Şahin et al. (31) investigated the relation of hs-CRP and Brain natriuretic peptide (BNP) levels with the atrial SEC in 84 permanent AF patients with different etiologies and showed that hs-CRP and BNP levels were significantly higher in mitral stenosis patients than in hyperthyroidism and in hypertensive patients (31). They also showed that hs-CRP levels were significantly related to the presence of mild-moderate SEC and thrombi, mainly in mitral stenosis patients. In the study of Kaya et al. (11), hs-CRP and NLR values in the SEC positive group were significantly higher than in our study. SEC staging was not done in both studies. This suggests that SEC degree may be greater in mitral stenosis patients compared to non-valvular AF patients, and the observed difference may arise from this distinction. Further studies including evaluation of SEC staging are needed to obtain clearer understanding of this phenomenon.

In the present study, hs-CRP [OR1.34 (1.09-1.65 95% CI) p=0.006], LA diameter [OR11.92 (1.84-77.07 95% CI) p=0.01], presence of SEC [OR5.40 (1.04-12.02 95% CI) p=0.045] and systolic BP [OR1.05 (1.01-1.10 95% CI) p=0.03] were found to be independent predictors of recurrence after a successful CV in non-valvular AF patients. While, LA diameters [OR11.92 (1.84-77.07 95% CI) p=0.01] and SEC presence [OR5.40 (1.04-12.02 95% CI) p=0.045] were the best predictors of recurrence in the multiple regression model, hs-CRP remains a significant predictor of recurrence in the regression model [OR1.34 (1.09-1.65 95% CI) p=0.006]. On the contrary, NLR was not found to be a significant factor in AF recurrence. A weak linear correlation was detected between CRP and NLR. In univariate analysis, while duration of AF is a predictor of AF recurrence, this predictive relationship disappears in multiple logistic regression analysis. The reason for this may be a close relationship between AF duration and LA diameter, inflammation severity, remodeling development, and SEC development. The statistical significance of the relationships observed in the univariate model was not present in multiple logistic regression analysis including all of these factors. Similarly, presence of DM has no predictive value for AF recurrence in our multiple logistic regression analysis.

Study limitations

The duration of follow-up was short. However, more than half of the incidence of recurrence develops within the first month after DC-CV (32). Therefore we consider this limitation to be acceptable. In addition, the use of ECG for definition of recurrence is a major limitation. More accurate results could have been obtained with PAF screening using 72 -hour Holter records. Routine 72-hour Holter monitoring could not be performed due to cost.

Conclusion

Neutrophil/lymphocyte ratio is insufficient for prediction of recurrence after DC-CV in persistent AF patients. Hs-CRP is still a good inflammatory marker for indicating recurrence. Because of the ease of calculation and low cost, the role of NLR in predicting development and recurrence of AF in different clinic settings should be investigated in future prospective studies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - A.A., H.A., M.K., M.Y., K.Ö., H.G.; Design - A.A., H. A., M.K., M.Y., K.Ö., H.G.; Supervision - A.A., M.K., E.E.G., M.Y., H.A., K.Ö.; Resource - A.D., H.A., H.G.; Materials - E.E.G., H.A., Ç.D.; Data Collection&/or Processing - A.A., H.A., K.D., H.A., E.E.G., K.D.; Analysis&/or Interpretation - A.A., H.A., M.K.; Literature Search - A.A., H.A., K.D., M.K., Ç.D.; Writing - A.A., H.A., M.K.; Critical Reviews - A.A., H.A., M.K., K.Ö., H.G.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98: 946-52. [CrossRef]
2. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH. Pharmacological Intervention in Atrial Fibrillation (PIAF) Study Investigators. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J 2003; 24: 1430-6. [CrossRef]
3. Spodick DH. Arrhythmias during acute pericarditis. A prospective study of 100 consecutive cases. JAMA 1976; 235: 39-41. [CrossRef]
4. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: post- surgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997; 96: 3542-8. [CrossRef]
5. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. Am J Cardiol 2005; 95: 764-7. [CrossRef]
6. Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, et al. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J 2004; 45: 441-5. [CrossRef]
7. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. Int J Cardiol 2006; 108: 346-53. [CrossRef]
8. Shen XH, Chen Q, Shi Y, Li HW. Association of neutrophil/lymphocyte ratio with long-term mortality after ST elevation myocardial infarction treated with primary percutaneous coronary intervention. Chin Med J 2010; 123: 3438-43.
9. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta 2008; 395: 27-31. [CrossRef]
10. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010; 105: 186-91. [CrossRef]
11. Kaya MG, Akpek M, Elçik D, Kalay N, Yarlioğlueş M, Koç F, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers. Am J Cardiol 2012; 109: 851-5. [CrossRef]
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report. JAMA 2003; 289: 2560-72. [CrossRef]
13. Schmidt M, Rieber J, Daccarett M, Marschang H, Sinha AM, Biggar P, et al. Relation of recurrence of atrial fibrillation after successful cardioversion to renal function. Am J Cardiol 2010; 105: 368-72. [CrossRef]
14. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler quantification task force of the nomenclature and standards committee of the American society of echocardiography. recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American society of echocardiography. J Am Soc Echocardiogr 2002; 15: 167-84. [CrossRef]
15. Wu ZK, Laurikka J, Vikman S, Nieminen R, Moilanen E, Tarkka MR. High postoperative interleukin-8 levels related to atrial fibrillation in patients undergoing coronary artery bypass surgery. World J Surg 2008; 32: 2643-9. [CrossRef]
16. Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. Am J Cardiol 2004; 93: 1176-8. [CrossRef]
17. Uçar HI, Tok M, Atalar E, Doğan OF, Öç M, Farsak B, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. Heart Surg Forum 2007; 10: E131-5. [CrossRef]
18. Rienstra M, Sun JX, Magnani JW, Sinner MF, Lubitz SA, Sullivan LM, et al. White blood cell count and risk of incident atrial fibrillation (from the Framingham Heart Study). Am J Cardiol 2012; 109: 533-7. [CrossRef]
19. Fujiki A, Sakamoto T, Nishida K, Mizumaki K, Inoue H. Relation of interleukin-6 and C-reactive protein levels to sinus maintenance after pharmacological cardioversion in persistent atrial fibrillation. J Cardiovasc Pharmacol 2007; 50: 264-6. [CrossRef]
20. Rizos I, Tsiodras S, Rigopoulos AG, Dragomanovits S, Kalogeropoulos AS, Papathanasiou S, et al. Interleukin-2 serum levels variations in recent onset atrial fibrillation are related with cardioversion outcome. Cytokine 2007; 40: 157-64. [CrossRef]
21. Özaydın M, Erdoğan D, Tayyar S, Uysal BA, Doğan A, İçli A, et al. N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study. Anadolu Kardiyol Derg 2011; 11: 305-9.
22. Malouf JF, Kanagala R, Al Atawi FO, Rosales AG, Davison DE, Murali NS, et al. High sensitivity C-Reactive protein a novel predictor for recurrence of atrial fibrillation after successful cardioversion. J Am Coll Cardiol 2005; 46: 1284-7. [CrossRef]
23. Çelebi OO, Çelebi S, Canbay A, Ergün G, Aydoğdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. Cardiology 2011; 118: 168-74. [CrossRef]
24. Alkhouri N, Morris-Stiff G, Campbell C, Lopez R, Tamimi TA, Yerian L, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012; 32: 297-302. [CrossRef]
25. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 2007; 73: 215-20. [CrossRef]
26. Akpek M, Kaya MG, Lam YY, Şahin O, Elçik D, Çelik D, et al. Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated

myocardial infarction undergoing primary coronary intervention. Am J Cardiol 2012; 110: 621-7. [CrossRef]
27. Chatterjee S, Chandra P, Guha G, Kalra V, Chakraborty A, Frankel R. Pre-procedural elevated white blood cell count and neutrophil-lymphocyte (N/L) ratio are predictors of ventricular arrhythmias during percutaneous coronary intervention. Cardiovasc Hematol Disord Drug Targets 2011 Oct 26. [Epub ahead of print] [CrossRef]
28. Chelazzi C, Villa G, De Gaudio AR. Postoperative atrial fibrillation. ISRN Cardiol 2011; 2011:203179.
29. Muhmmed Suliman MA, Bahnacy Juma AA, Ali Almadhani AA, Pathare AV, Alkindi SS, Uwe Werner F. Predictive value of neutrophil to lymphocyte ratio in outcomes of patients with acute coronary syndrome. Arch Med Res 2010; 41: 618-22. [CrossRef]
30. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008; 102: 653-7. [CrossRef]
31. Şahin T, Acar E, Çelikyurt U, Kılıç T, Kozdağ G, Ağaçdiken A, et al. Relation of hs-CRP and BNP levels with the atrial spontaneous echo contrast and thrombi in permanent atrial fibrillation patients with different etiologies. Med Sci Monit 2012; 18: CR78-87.
32. Tieleman RG, Van Gelder IC, Crijns HJ, De Kam PJ, Van Den Berg MP, Haaksma J, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998; 31: 167-73. [CrossRef]