ORIGINAL ARTICLE

Association of neutrophil/lymphocyte ratio and CHA_2DS_2-VASc score with left atrial thrombus in patients who are candidates for percutaneous mitral balloon valvuloplasty

Nötrofil lenfosit oranı ve CHA_2DS_2-VASc risk puanlamasının perkütan mitral balon valvüloplastiye aday hastalardaki sol atriyal pıhtı ile ilişkisi

Orhan Maden, M.D., Kevser G. Balci, M.D., Mustafa M. Balci, M.D., Serdar Kuyumcu, M.D., Hatice Selçuk, M.D., Mehmet T. Selçuk, M.D.

Department of Cardiology, Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: Association between inflammation and pro-thrombotic state has been described previously. Aim of the present study was to investigate if presence of left atrial (LA) thrombus or spontaneous echocardiographic contrast (SEC) in rheumatic mitral stenosis (MS) was related to neutrophil/lymphocyte ratio (NLR), and to determine predictive utility of the CHA_2DS_2-VASc risk stratification score in patients with mitral stenosis complicated by LA thrombus.

Methods: NLR and CHA_2DS_2-VASc score of 188 patients with MS and 35 healthy controls were evaluated. All analyses were also conducted according to rhythm status, excluding control group.

Results: Among patients with MS, there were 31 patients in thrombus-positive group, 142 patients in SEC-positive group, and 15 patients in thrombus/SEC-negative group. Among patients with MS and sinus rhythm (SR) (n=105; 55.8%); 9.5% of them had LA thrombus, and 78% of them had SEC. In the SR group, median NLR was significantly higher in thrombus-positive group compared with thrombus/SEC-negative and control groups (p<0.001). Among patients with MS and atrial fibrillation (AF); there was no significant difference regarding NLR according to thrombus and SEC presence (p=0.214). In both SR and AF groups, there was no significant difference according to SEC/thrombus presence regarding median CHA_2DS_2-VASc score (p>0.05).

Conclusion: Elevated NLR is related to presence of LA thrombus in patients with MS and SR. The utility of CHA_2DS_2-VASc score in patients with MS and SR complicated by LA thrombus is debatable, according to our results.

ÖZET

Amaç: Enflamasyon ve pıhtılaşmaya yatkınlık arasındaki ilişki daha önce tanımlanmıştır. Biz bu çalışmada, romatizmal mitral darlığında sol atriyal pıhtı ve spontan eko kontrast (SEK) varlığının nötrofil lenfosit oranı (NLO) ile ilişkisini ve CHA_2DS_2-VASc risk puanlamasının mitral darlığı olan hastalarda sol atriyal pıhtı varlığını öngördürmedeki kullanılırlığını araştırdık.

Yöntemler: Mitral darlığı bulunan 188 hastada ve 35 sağlıklı kontrol olgusunda NLO ve CHA_2DS_2-VASc risk puanlamasını değerlendirdik. Kontrol grubu hariç, bütün değerlendirmeler ayrıca ritim durumuna göre de yapıldı.

Bulgular: Mitral darlığı bulunan hastaların 31'inde sol atriyal pıhtı ve 142'sinde de SEK mevcuttu, 15 hastada ise pıhtı ya da SEK izlenmedi. Ritim durumuna göre mitral darlıklı hastalar ikiye ayrıldığında; sinüs ritmi (SR) olan hastaların (n=105, 55.8%); %9.5'inde sol atriyal pıhtı ve %78'inde SEK mevcuttu. Sinüs ritminde olan grupta; medyan NLO pıhtı-pozitif olan grupta diğer gruplara göre anlamlı derecede yüksekti (p<0.001). Atriyum fibrilasyonu (AF) olan hastalarda; NLO pıhtı ya da SEK varlığına göre farklılık göstermedi (p=0.214). Medyan CHA_2DS_2-VASc puanı pıhtı ya da SEK varlığına göre yine bütün gruplarda anlamlı farklılık göstermedi (p>0.05).

Sonuç: Artmış NLO sinüs ritmindeki mitral darlıklı hastalarda sol atriyal pıhtı varlığı ile ilişkilidir. Sonuçlarımıza göre CHA_2DS_2-VASc risk puanlamasının mitral darlığında sol atriyal pıhtı varlığını öngördürmedeki yararı tartışmalıdır.

Received: May 23, 2016 *Accepted:* March 27, 2017

Correspondence: Dr. Kevser G Balci. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Turkey.
Tel: +90 312 - 306 11 28 e-mail: kevs84@gmail.com

Rheumatic fever (RF) is an autoimmune disorder that is mostly seen in developing countries. Rheumatic mitral valve disease (RMVD) is major sequela of RF.[1] Symptomatic patients with severe-to-moderate mitral stenosis (MS) and favorable valve morphology are candidates for percutaneous mitral balloon valvuloplasty (PMBV).[2] However, MS is frequently complicated by left atrial (LA) thrombus, which is important limitation for PMBV and a potential precursor for embolization.[3]

CHA_2DS_2-VASc (congestive heart failure, history of hypertension, age, diabetes mellitus, history of stroke/transient ischemic attack/embolic event, vascular disease, female gender) score predicts thromboembolic events in patients with nonvalvular atrial fibrillation (AF).[4] In patients with MS and sinus rhythm (SR), this scoring system is not routinely used to determine risk of thromboembolism. There are scant data about ability of CHA_2DS_2-VASc score to predict LA thrombosis in such patients. However, if AF occurs, regardless of the CHA_2DS_2-VASc score, patients are treated with oral anticoagulant (OAC) therapy because structurally changed LA confers higher embolic risk profile.[5,6]

Neutrophil/lymphocyte ratio (NLR), calculated as absolute count of neutrophils divided by absolute count of lymphocytes, is a well-studied systemic inflammation indicator that can be easily obtained from white blood cell count. Previously, NLR was found to be related to severity of mitral valve disease[7,8] and presence of spontaneous echocardiographic contrast (SEC).[9,10] Hence, it was thought that RMVD might be a chronic inflammatory disease[11] and association between inflammation and pro-thrombotic state was previously described.[12] In this study, primary endpoint was to determine if presence of LA thrombus or SEC in MS was related to NLR, and if CHA_2DS_2-VASc score could predict LA thrombus in patients with MS and SR. Secondary endpoint was to evaluate differences in NLR and CHA_2DS_2-VASc scores according to rhythm status.

Abbreviations:

AF	*Atrial fibrillation*
CHA_2DS_2-VASc	*Congestive heart failure, history of hypertension, age, diabetes mellitus, history of stroke/transient ischemic attack/embolic event, vascular disease, female gender*
CRP	*C-reactive protein*
LA	*Left atrial*
mMVG	*Mean mitral valve gradient*
MS	*Mitral stenosis*
NLR	*Neutrophil/lymphocyte ratio*
OAC	*Oral anticoagulant*
PMBV	*Percutaneous mitral balloon valvuloplasty*
RF	*Rheumatic fever*
RMVD	*Rheumatic mitral valve disease*
SEC	*Spontaneous echocardiographic contrast*
SR	*Sinus rhythm*
TEE	*Transesophageal echocardiogram*
TTE	*Transthoracic echocardiogram*

METHODS

Study population

Total of 188 consecutive patients from January 2005 to March 2014 who had severe-to-moderate MS and were candidates for PMBV were enrolled retrospectively in the present study. Control group consisted of 35 age- and sex-matched healthy participants (5 men, 30 women; mean age 42.8±15.0 years). Exclusion criteria were as follows: additional significant valvular heart disease requiring treatment, chronic inflammatory disease, hematological disorder, and renal or hepatic disorder (n=11). Study participants were divided into 4 groups: Group 1, patients with LA thrombus; Group 2, patients with SEC; Group 3, patients without LA thrombus/SEC; and Group 4, healthy controls. Age, gender, NLR, and CHA_2DS_2-VASc scores of patient and control groups were compared. In the patient groups, all analyses were also performed according to rhythm status. All patients with MS underwent transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) evaluation prior to PMBV. TTE was also used on all healthy controls to determine eligibility for the study. Blood samples were collected after fasting period of 8 hours. Automated blood cell counter (Siemens ADVIA 2120i Hematology System; Siemens Healthineers, GmbH, Erlangen, Germany) was used to measure total and differential leukocyte counts. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. Electronic medical records were used to obtain participants' medical histories. Research protocol was approved by the local ethics committee of Turkiye Yuksek Ihtisas Research and Education Hospital.

Echocardiographic assessment

All study participants underwent comprehensive 2-dimensional and color Doppler TTE (Vivid 7 Ultrasound System; GE Healthcare, Inc. Chicago, IL, USA) at rest in left lateral position. LA diameter was evaluated with M-mode in parasternal long axis view

according to American Society of Echocardiography guidelines. Mitral valve area was measured using planimetric method in parasternal short axis view at end systole. Continuous wave Doppler was used to determine mean mitral valve gradient (mMVG). Semiquantitative evaluation of MR (mild, moderate, or severe) was performed with color flow mapping in parasternal long axis and apical 4-chamber views. Valve morphology was assessed using Wilkins[13] echo scoring system. Systolic pulmonary artery pressure was calculated using peak pressure gradient of tricuspid regurgitation according to Bernoulli equation, and then assumed right atrial pressure was (10 mmHg) added. Under local pharyngeal anesthesia (1% lidocaine spray) and intravenous diazepam, TEE assessment was obtained using the same system with a 5-MHz transducer. An experienced cardiologist determined eligibility for PMBV and presence of LA thrombus (either located in the LA appendix or attached to the LA wall). Left atrial spontaneous echo contrast was evaluated according to previously reported criteria.[14]

CHA_2DS_2-VASc score calculation

All patients were evaluated with original scoring system to calculate CHA_2DS_2-VASc score: congestive heart failure (1 point); history of hypertension (1 point); age (2 points for ≥75 years, 1 point for age >65 to <75 years); diabetes mellitus (1 point); history of stroke, transient ischemic attack, embolic event (2 points); vascular disease (1 point); female gender (1 point).[4] Scores ranging from 0 to 9 were noted, and highest score conferred highest thromboembolic risk.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Normal distribution of continuous variables was determined using Kolmogorov-Smirnov test, and homogeneity of variances was evaluated with Levene's test. Continuous variables were reported as mean±SD or median (min-max), as applicable.

Difference in mean age between groups was analyzed with one-way analysis of variance test (ANOVA). Differences between groups in non-normally distributed data were compared using Mann-Whitney U test; Kruskal-Wallis test was applied for comparisons between more than 2 independent groups. When p value from one-way ANOVA or Kruskal-Wallis test was statistically significant, post hoc Tukey's honest significant difference test or Conover's non-parametric multiple comparison test was used to determine which group differed from the others. Categorical data were analyzed with likelihood ratio test. Best predictor(s) for presence of SEC/LA thrombus in SR group were determined by multiple logistic regression analyses. Any variable whose univariable test had p value less than 0.25 was accepted as candidate for multivariable model along with all variables of known clinical importance. P value less than 0.05 was considered statistically significant. For all possible multiple comparisons, Bonferroni correction was applied to control Type I error.

RESULTS

Total of 188 patients with MS and 35 healthy control participants were enrolled in this study. Among patients with MS, 105 (55.8%) patients were in SR and 83 (44.2%) were in AF. LA thrombus was found in 31 (16.4%) patients, and all were located in LA appendix. Of these patients, 10 (32.2%) were in SR. SEC was observed in 142 (75.5%) patients, and 82 (57.7%) of them were in SR. Among patients with MS and SR, thrombus was detected 9.5% and SEC was detected 78% of them.

Table 1 illustrates comparison of baseline and echocardiographic characteristics of the groups according to SEC/thrombus presence. Thrombus-positive patients were significantly older than members of the other study groups (p=0.003), but number of female patients did not differ between groups (p=0.099). Additionally, valvular score was greater in thrombus-positive group than in SEC-positive and thrombus/SEC-negative groups (thrombus-positive group: median 9 points vs SEC-positive and thrombus/SEC-negative groups: median 8 points; p<0.001). Mitral regurgitation grade was higher in SEC-positive and thrombus/SEC-negative groups than in thrombus-positive group (p=0.005). LA diameter was significantly smaller in thrombus/SEC-negative group compared with SEC and thrombus-positive groups (p=0.002). NLR and number of patients with CHA_2DS_2-VASc ≥2 did not differ between all groups (p=0.112 and p=0.804, respectively).

Table 2 demonstrates additional analyses according to rhythm status. In SR group, patients with thrombus were older than those without thrombus (p=0.007)

Table 1. Baseline characteristics according to presence of spontaneous echocardiographic contrast or thrombus

Variables	SEC (+)	Thrombus (+)	Thrombus/SEC (–)	Control	p
Age, years	44.5±11.4[b,d]	52.5±9.6[a,b,c]	34.5±9.6[a,d]	42.8±15.0[c]	0.003‡
Female, n (%)	119 (83.8)	21 (67.7)	13 (86.7)	35 (85.7)	0.099¶
Neutrophil/lymphocyte ratio	2.2 (1.0–9.2)	2.6 (1.2–8.3)	1.8 (1.1–5.6)	1.7 (0.9–3.4)	0.112Φ
CHA_2DS_2-VASc ≥2, n (%)	80 (80.8)	15 (15.1)	4 (4)	7 (33.3)	0.804¶
Mean valvular gradient (mmHg)	11 (5–25)	10 (5–16)	11 (5–27)	–	0.059Φ
Mitral valve area (cm^2)	1.2 (0.8–1.7)	1.2 (0.8–1.9)	1.1 (0.9–1.4)	–	0.268Φ
sPAP (mmHg)	47 (27–100)	45 (35–80)	45 (30–60)	–	0.813Φ
Left atrium (cm)	4.6 (3.6–6.2)[d]	4.9 (3.5–6.2)[a]	4.4 (3.4–4.7)[a,d]	–	0.002Φ
Mitral regurgitation	1 (1–3)[b]	1 (1–2)[a,b]	1 (1–2)[a]	–	0.005Φ
Valvular score	8 (5–11)[b]	9 (6–12)[a,b]	8 (5–10)[a]	–	<0.001Φ

‡One-way analysis of variance; ¶Likelihood Ratio test; ΦKruskal Wallis test; a: Difference between Thrombus (+) and Thrombus/SEC (–) groups is significant (p<0.05), b: Difference between SEC (+) and Thrombus (+) groups is significant (p<0.05), c: Difference between Thrombus (+) and control groups is significant (p<0.01), d: Difference between Thrombus/SEC (–) and SEC (+) groups is significant (p<0.05). CHA_2DS_2-VASc: Congestive heart failure; history of hypertension; age; diabetes mellitus; history of stroke/TIA/embolic event; vascular disease; female gender; SEC: Spontaneous echocardiographic contrast; sPAP: Systolic pulmonary artery pressure.

and patients with LA thrombus were more likely to be men when compared with SEC-positive, thrombus/SEC-negative and control groups (p<0.001, p=0.039, p=0.007, respectively). When patients with MS and SR were compared with patients with MS and AF, there was no significant difference in NLR (p=0.138). In SR group, median NLR was significantly higher in thrombus-positive group compared with thrombus/SEC-negative and control groups (p<0.001); median NLR was also significantly higher in SEC-positive group when compared with control group (p<0.001). In AF group, there was no significant difference regarding NLR according to presence of thrombus and SEC (p=0.214) (Figure 1, 2). In both SR and AF

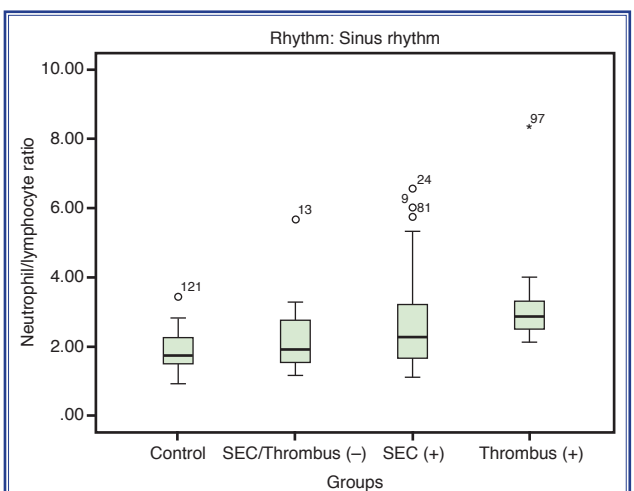

Figure 1. Comparison of neutrophil/lymphocyte ratio (NLR) level in patients with sinus rhythm according to presence of left atrial spontaneous echocardiographic contrast or thrombus. The horizontal lines in the middle of each box indicate the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the maximum and minimum NLR levels. Open circles indicate outliers. Asterisks represent extreme cases.

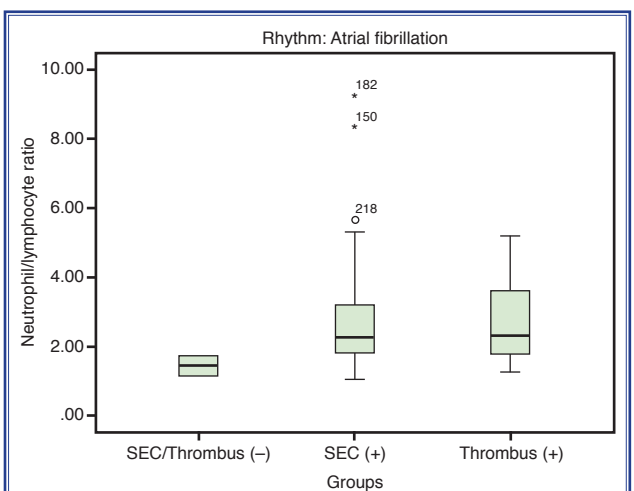

Figure 2. Comparison of neutrophil/lymphocyte ratio (NLR) level in patients with atrial fibrillation according to presence of left atrial spontaneous echocardiographic contrast or thrombus. The horizontal lines in the middle of each box indicate the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the maximum and minimum NLR levels. Open circles indicate outliers. Asterisks represent extreme cases.

Table 2. Baseline characteristics according to spontaneous echocardiographic contrast or thrombus presence and rhythm status

Variables	SEC (+)	Thrombus (+)	Thrombus/SEC (–)	Control	p†
Age, years					
Sinus rhythm	42.1±11.2	52.4±10.6a	34.3±10.4[a]	42.8±15.0	0.007‡
Atrial fibrillation	47.9±11.0	52.6±9.5	36.0±0.0	–	0.054‡
Female, n (%)					
Sinus rhythm	73 (89.0%)[b]	4 (40.0%)[a,b,c]	11 (84.6%)[a]	35 (85.7%)[c]	0.008¶
Atrial fibrillation	46 (76.6%)	17 (80.9%)	2 (100.0%)	–	0.560¶
Neutrophil/lymphocyte ratio					
Sinus rhythm	2.3 (1.1–6.6)[d]	2.8 (2.1–8.3)[a,c]	1.9 (1.1–5.7)[a]	1.7 (0.9–3.4)[c,d]	<0.001Φ
Atrial fibrillation	2.2 (1.0–9.3)	2.3 (1.2–5.2)	1.4 (1.1–1.7)	–	0.214Φ
CHA_2DS_2-VASc ≥2, n (%)					
Sinus rhythm	35 (42.7%)	4 (40.0%)	2 (15.4%)	7 (33.3%)	0.242¶
Atrial fibrillation	45 (75.0%)	11 (52.4%)	2 (100.0%)	–	0.081¶
Mean valvular gradient (mmHg)					
Sinus rhythm	11 (5–25)	10 (5–14)	11 (5–27)	–	0.417Φ
Atrial fibrillation	11 (6–20)	10 (7–16)	12.5 (10–15)	–	0.170Φ
Mitral valve area (cm^2)					
Sinus rhythm	1.1 (0.8–1.5)	1.1 (0.8–1.4)	1.1 (0.9–1.4)	–	0.604Φ
Atrial fibrillation	1.2 (0.8–1.7)	1.3 (1.0–1.9)	1.2 (1.1–1.3)	–	0.128Φ
sPAP (mmHg)					
Sinus rhythm	45 (33–85)	44 (35–50)	48 (30–65)	–	0.464Φ
Atrial fibrillation	48 (27–100)	50 (35–80)	40 (35–45)	–	0.366Φ
Mitral regurgitation					
Sinus rhythm	1 (1–3)	1 (1–2)	1 (1–2)	–	0.722Φ
Atrial fibrillation	1 (1–3)[b]	1 (1–2)[b]	1 (1–1)	–	0.020Φ
Valvular score					
Sinus rhythm	8 (5–11)	9 (6–11)	8 (5–10)	–	0.181Φ
Atrial fibrillation	8 (5–11)	10 (8–12)	7 (6–8)	–	0.044Φ
Left atrium (cm)					
Sinus rhythm	4.5 (3.6–5.7)	5.0 (3.5–6.2)	4.4 (3.4–4.7)	–	0.035Φ
Atrial fibrillation	4.9 (4.0–6.2)	4.7 (3.7–6.2)	3.9 (3.4–4.5)	–	0.164Φ

†According to Bonferroni adjustment value of p<0.025 was accepted as significant, ‡One-way analysis of variance, ¶Likelihood ratio test, ΦKruskal Wallis test, a: Difference between Thrombus (+) and Thrombus/SEC (–) groups is significant (p<0.025), b: Difference between SEC (+) and Thrombus (+) groups is significant (p<0.025), c: Difference between Thrombus (+) and Control groups is significant (p<0.025), d: Difference between SEC (+) and Control groups is significant (p<0.001). SEC: Spontaneous echocardiographic contrast; sPAP: Systolic pulmonary artery pressure. CHA_2DS_2-VASc: Congestive heart failure; history of hypertension; age; diabetes mellitus; history of stroke/TIA/embolic event; vascular disease; female gender.

groups, median CHA_2DS_2-VASc score did not differ according to thrombus and SEC presence (p=0.129, p=0.241, respectively). When CHA_2DS_2-VASc ≥2 points was accepted as high score, number of patients with high score did not differ according to rhythm status (SR: p=0.242; AF: p=0.081). When the patients were divided into 2 groups according to CHA_2DS_2-VASc score (low-intermediate-risk group: 0-1 point vs high-risk group: ≥2 points), median NLR did not differ according to rhythm status (SR: p=0.682; AF: p=0.929) (Table 3). When all patients were grouped according to rhythm status, median CHA_2DS_2-VASc score was significantly higher in AF group compared with SR group (p<0.001) (Table 4). Also, SEC-posi-

Table 3. NLR according to CHA_2DS_2-VASc score and rhythm status

CHA_2DS_2-VASc	NLR	p†
Sinus rhythm		0.682
0–1	2.3 (0.9–6.6)	
2+	2.1 (1.1–8.3)	
Atrial fibrillation		0.929
0–1	2.3 (1.0–5.7)	
2+	2.2 (1.1–9.3)	

†Mann-Whitney U-test. NLR: Neutrophil/lymphocyte ratio, CHA_2DS_2-VASc: Congestive heart failure; history of hypertension; age; diabetes mellitus; history of stroke/transient ischemic attack/embolic event; vascular disease; female gender.

tive group with AF had greater CHA_2DS_2-VASc score than patients with SEC and SR (p<0.001). Among patients with thrombus, CHA_2DS_2-VASc score did not differ according to rhythm status (p=0.217). In patients with CHA_2DS_2-VASc score of 0, there were 6 patients with SEC and 3 patients with LA thrombus. In thrombus-positive patients, 2 were in SR. In multiple logistic regression analysis, age was the only parameter related to presence of SEC/LA thrombus in SR group (odds ratio, 1.070; 95% confidence interval, 1.006-1.138; p=0.031).

DISCUSSION

The present study has demonstrated that median CHA_2DS_2-VASc score was significantly higher in AF group when compared with SR group in patients with MS. However, CHA_2DS_2-VASc score did not differ according to presence of thrombus/SEC. Among patients with SR, median NLR was significantly higher in thrombus-positive group compared with thrombus/SEC-negative and control groups, but NLR did not differ according to rhythm status.

Systemic inflammation serves a function in the pathogenesis and outcomes of various disease processes. It is still a subject of debate if acute infection and the subsequent healing process in rheumatic valvular disease are only short-lived, or if there is an ongoing inflammation after the acute event that is responsible for disease progression.[15,16] In previous research, increased level of circulating adhesion molecules in rheumatic MS has been reported,[17] and elevated C-reactive protein (CRP) level has been demonstrated in RMVD.[15] Guilherme et al. described predominant secretion of interferon gamma and tumor necrosis factor alpha, type 1 T helper cytokines from intralesional mononuclear cells in heart lesions in both acute RF and chronic rheumatic heart disease. Furthermore, they claimed that even in chronic phase of RMVD there was heart-driven autoimmune reaction.[11] Similarly, Schoen et al. found marked leukocyte infiltration in pathological specimens of rheumatic mitral valves.[18]

NLR, which is a general indicator of systemic inflammation, represents the balance between neutrophil and lymphocyte counts in the body.[9] During inflammatory reactions, count of subtypes of white blood cells and balance between them change as result of decreased production of lymphocyte counts. Accordingly, several studies have focused on the as-

Table 4. CHA_2DS_2-VASc score and NLR in SEC-positive, thrombus-positive groups, and all patients

	SEC (+)	Thrombus (+)	All patients
Neutrophil/lymphocyte ratio			
Sinus rhythm	2.3 (1.1–6.6)	2.8 (2.1–8.3)	2.1 (0.9–8.3)
Atrial fibrillation	2.2 (1.0–9.3)	2.3 (1.2–5.2)	2.2 (1.0–9.3)
p-value†	0.507‡	0.217‡	0.138¶
CHA_2DS_2-VASc			
Sinus rhythm	1 (0–4)	1 (0–2)	1 (0–4)
Atrial fibrillation	2 (0–7)	2 (0–5)	2 (0–7)
p-value†	<0.001‡	0.217‡	<0.001¶

†Mann-Whitney U test; ‡according to Bonferroni adjustment value of p<0.025 was accepted as significant, ¶a value of p<0.05 was accepted as significant. CHA_2DS_2-VASc: Congestive heart failure; history of hypertension; age; diabetes mellitus; history of stroke/transient ischemic attack/embolic event; vascular disease; female gender; SEC: Spontaneous echocardiographic contrast.

sociation between elevated NLR and MS.[7–10] Both Akboğa et al. and Polat et al. found that patients with MS had higher NLR level than healthy individuals.[7,8] Similarly, we found that NLR was significantly higher in patients with MS than in control group. Interestingly, between SR and AF groups, there was no significant difference with regard to NLR. Although rhythm status did not alter NLR, we think that higher NLR in patients with MS compared with healthy participants may indicate an ongoing inflammatory process, which is consistent with previous reports.

Platelet activation and inflammatory response may provoke worse outcomes in cardiovascular disease. Although relationship between inflammation and prothrombotic state has been described in several reports,[12,19] exact mechanism behind thrombogenesis is not fully understood. Conway et al. found increased level of interleukin-6 and CRP, as well as greater plasma viscosity in patients with chronic AF compared with healthy controls. They reported that inflammation had possible role in prothrombotic state of AF.[12] In patients with MS, Kaya et al. and Öztürk et al. demonstrated relationship between SEC and NLR, and both suggested link between inflammation and prothrombotic state.[9,10] Similarly, in SR group, we found elevated NLR level in thrombus-positive group compared with thrombus/SEC-negative and control groups. In rheumatic MS, combination of inflammatory response and platelet activation may aggravate prothrombotic process. Therefore, elevated NLR may signify an active inflammation and resultant tendency to thrombosis. MS is frequently associated with LA clots, and incidence is higher in older patients with more severe stenosis, lower cardiac output, and AF.[20] Patients with MS and SR also carry risk for LA clot formation, and increasing age, LA dilatation, mMVG, and dense SEC are mostly responsible for thrombus formation.[21] Goswami et al. demonstrated that larger LA size and presence of SEC positively correlated with LA clot in subgroup of patients with rheumatic MS and SR.[22] Therefore, LA thrombus may be predicted by both echocardiographic predictors (LA diameter, age, mMVG, presence of SEC) and laboratory tests. As percentage of patients having LA thrombus is relatively high in SR (2.4–13.5%),[21] early identification may be necessary to start an anticoagulant therapy. Consistent with previous data, we found that 9.5% of patients in SR group had LA thrombus. Notably, among all patients, there was not a significant difference between AF and SR groups regarding NLR. Possibly, duration of AF might also alter inflammatory response,[12] but in the present study we did not have data regarding AF duration.

CHA_2DS_2-VASc score is a clinical thromboembolic risk score for predicting high-risk patients who can benefit from OAC therapy for stroke prevention in nonvalvular AF. In AF, bleeding risk with OAC causes significant morbidity and mortality, so adequate risk stratification is important to determine the patients who have stroke risk and to guide decision to implement OAC therapy. Conversely, patients with RMVD and AF are advised to use OAC regardless of estimated CHA_2DS_2-VASc score due to higher embolic risk.[5,6] Clinical utility of CHA_2DS_2-VASc score in nonvalvular atrial flutter to predict LA clot has been investigated and sensitivity of higher CHA_2DS_2-VASc score for LA thrombus was found to be greater, but not significant.[23] In a study conducted by Zoppo et al., higher CHA_2DS_2-VASc score and larger LA size predicted LA thrombus in warfarin-treated patients with AF.[24] However, ability of CHA_2DS_2-VASc score to predict LA clot in patients with MS was not investigated thoroughly. In a previous study, Ozturk et al. observed higher CHA_2DS_2-VASc score among patients with MS and LA thrombus than in patients without thrombus. CHA_2DS_2-VASc score appeared to predict LA thrombosis in univariate analysis, but not in multivariate analysis.[25] We did not find a significant difference between thrombus-positive, thrombus/SEC-negative, and SEC-positive groups regarding median CHA_2DS_2-VASc score in either SR or AF group. Also, in our study, there was not a significant correlation between NLR and CHA_2DS_2-VASc score in thrombus-positive and SEC-positive patients in both AF and SR groups. When we separated patients into low-intermediate-risk and high-risk groups according to CHA_2DS_2-VASc score, median NLR did not differ in SR and AF groups. Notably, we observed SEC in 6 patients and LA thrombus in 3 patients whose CHA_2DS_2-VASc scores were 0. Moreover, 2 of the thrombus-positive patients were in SR. However, unlike study conducted by Ozturk et al., we also included patients with AF. The distinct results between the 2 studies might be result of different features of the selected patients. According to our study, in patients with MS and SR, ability of CHA_2DS_2-VASc score to anticipate which patients might benefit early OAC medication is low.

Limitations

This study has several limitations. First, it had a retrospective design and a relatively small sample size. Second, intermittent AF could not be ruled out in MS patients with SR. However, all patients in this study were followed-up in our hospital outpatient clinics for at least 1 year, and medical records were searched for AF. Those patients were not included in the study. Third, additional inflammation and thrombosis markers were not evaluated to address other confounding factors. And finally, rather than follow-up values, we only used spot NLR values.

Conclusion

NLR is a simple, objective, and less clinician-dependent hematological parameter that can be easily obtained from laboratory tests. This simple parameter is related to the presence of LA thrombus in patients with MS. Although we found higher CHA_2DS_2-VASc score in patients with MS and AF when compared with SR group, utility of CHA_2DS_2-VASc score in such patients is debatable, according to our results. Elevated NLR may be helpful to identify LA thrombus in patients with MS and SR.

Conflict-of-interest: None declared

REFERENCES

1. Ray R, Chambers J. Mitral valve disease. Int J Clin Pract 2014;68:1216–20. [CrossRef]
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185. [CrossRef]
3. Vigna C, de Rito V, Criconia GM, Russo A, Testa M, Fanelli R, et al. Left atrial thrombus and spontaneous echo-contrast in nonanticoagulated mitral stenosis. A transesophageal echocardiographic study. Chest 1993;103:348–52. [CrossRef]
4. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–72. [CrossRef]
5. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360–420. [CrossRef]
6. Hughes M, Lip GY; Guideline Development Group, National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care, National Institute for Health and Clinical Excellence. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost 2008;99:295–304. [CrossRef]
7. Akboğa MK, Akyel A, Şahinarslan A, Yayla Ç, Alsancak Y, Gökalp G, et al. Neutrophil-to-lymphocyte ratio is increased in patients with rheumatic mitral valve stenosis? Anatol J Cardiol 2015;15:380–4. [CrossRef]
8. Polat N, Yildiz A, Yuksel M, Bilik MZ, Aydin M, Acet H, et al. Association of neutrophil-lymphocyte ratio with the presence and severity of rheumatic mitral valve stenosis. Clin Appl Thromb Hemost 2014;20:793–8. [CrossRef]
9. Kaya MG, Akpek M, Elcik D, Kalay N, Yarlioglues M, Koc 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]
10. Öztürk D, Erturk M, Celik O, Ozyılmaz S, Akturk F, Cakmak HA, et al. The role of the neutrophil/lymphocyte ratio in patients with rheumatic mitral stenosis as an indicator of spontaneous echocardiographic contrast. Kardiol Pol 2014;72:969–76. [CrossRef]
11. Guilherme L, Cury P, Demarchi LM, Coelho V, Abel L, Lopez AP, et al. Rheumatic heart disease: proinflammatory cytokines play a role in the progression and maintenance of valvular lesions. Am J Pathol 2004;165:1583–91. [CrossRef]
12. Conway DS, Buggins P, Hughes E, Lip GY. Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. J Am Coll Cardiol 2004;43:2075–82. [CrossRef]
13. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60:299–308.
14. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994;23:961–9. [CrossRef]
15. Krasuski RA, Bush A, Kay JE, Mayes CE Jr, Wang A, Fleming J, et al. C-reactive protein elevation independently influences the procedural success of percutaneous balloon mitral valve commissurotomy. Am Heart J 2003;146:1099–104.
16. Catherine M. Otto, Robert O. Bonow. Valvular Heart Disease. In: Robert OB, Douglas LM, Douglas PZ, Peter L, editors. Braunwald's heart disease: a text book of cardiovascular medicine. 9th ed. Philadelphia: Elsevier Saunders; 2012. p. 1490–9.
17. Yetkin E, Erbay AR, Ileri M, Turhan H, Balci M, Cehreli S, et al. Levels of circulating adhesion molecules in rheumatic mitral stenosis. Am J Cardiol 2001;88:1209–11. [CrossRef]

18. Schoen FJ, St John Sutton M. Contemporary pathologic considerations in valvular disease. In: Virmani B, Atkinson JB, Feuoglio JJ, editors. Cardiovascular pathology. Philadelphia: Saunders; 1991. p.334–53.
19. Lip GY, 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. [CrossRef]
20. Kronzon I, Tunick PA, Glassman E, Slater J, Schwinger M, Freedberg RS. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. J Am Coll Cardiol 1990;16:1320–2.
21. Manjunath CN, Srinivasa KH, Panneerselvam A, Prabhavathi B, Ravindranath KS, Rangan K, et al. Incidence and predictors of left atrial thrombus in patients with rheumatic mitral stenosis and sinus rhythm: a transesophageal echocardiographic study. Echocardiography 2011;28:457–60. [CrossRef]
22. Goswami KC, Yadav R, Rao MB, Bahl VK, Talwar KK, Manchanda SC. Clinical and echocardiographic predictors of left atrial clot and spontaneous echo contrast in patients with severe rheumatic mitral stenosis: a prospective study in 200 patients by transesophageal echocardiography. Int J Cardiol 2000;73:273–9. [CrossRef]
23. Parikh MG, Aziz Z, Krishnan K, Madias C, Trohman RG. Usefulness of transesophageal echocardiography to confirm clinical utility of CHA2DS2-VASc and CHADS2 scores in atrial flutter. Am J Cardiol 2012;109:550–5. [CrossRef]
24. Zoppo F, Brandolino G, Berton A, Frigato N, Michieletto M, Zanocco A, et al. Predictors of left atrium appendage clot detection despite on-target warfarin prevention for atrial fibrillation. J Interv Card Electrophysiol 2012;35:151–8. [CrossRef]
25. Ozturk D, Celık O, Akın F, Akturk F, Aslan S, Ozyılmaz SO, et al. Usefulness of the uric acid and CHA2DS2-VASc score in prediction of left atrial thrombosis in patients with mitral stenosis and sinus rhythm. Cardiol J 2015;22:336–42. [CrossRef]

Keywords: Lymphocyte; mitral stenosis; neutrophil; thrombus.

Anahtar sözcükler: Lenfosit; mitral darlığı; nötrofil; pıhtı.