Dicle Tıp Dergisi / Dicle Med J (2020) 47 (1) : 24- 33

www.diclemedj.org

Original Article / Özgün Araştırma

New Uses of Platelet-Lymphocyte Ratio for Bleeding Risk Stratification in Patients with Nonvalvular Atrial Fibrillation: A Pilot Study

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Received: 05.08.2019; Revised: 23.12.2019; Accepted: 07.01.2020

Abstract

Objective: The primary aim of this study was to investigate the role of platelet-lymphocyte ratio (PLR) to predict bleeding risk in nonvalvular atrial fibrillation (NVAF). Secondary aim was to determine the possible relation between PLR and thromboembolic and bleeding risk scores. Tertiary aim was to evaluate the predictive value of PLR for the patients in the therapeutic international normalized ratio (INR) range.

Method: PLR was calculated from the complete blood count of 228 patients who were under warfarin management for NVAF. The patients were called and it was questioned whether they had experienced the bleeding event within six months after measurement of the PLR values.

Results: Bleeding event was observed in 48 patients after the PLR was calculated. It was found significantly correlation between PLR and CHA2DVAS2C ($p<0.01$) and HAS-BLED score ($p<0,001$). The ROC analysis showed that PLR predicted bleeding with a sensitivity of 83% and with a specificity of 84%, using a cut-off value of 165,9. The AUC (area under the curve) for the PLR was found 0.88 ($p<0.001$). PLR predicted the patients in therapeutic INR range with a sensitivity of 75% at ROC analysis, when using a cut-off value of 125,3 and AUC for the PLR was 0.73 ($p<0.001$). In the multivariate regression analysis, PLR>165,9 was determined significant indicator for bleeding ($p<0.001$) and showed more than a 12-fold increased risk of bleeding (12.27, [5.74-26.21]).

DOI: 10.5798/dicletip.705814
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Conclusions: The results of the present study indicate that the PLR might be a useful parameter to detect the risk of bleeding. To our knowledge, this is the first study demonstrating the correlation of PLR with both CHA2DS2-VASc and HAS-BLED risk scores. PLR may also predict the patients within the therapeutic INR range.

***Keywords**:* Platelet-Lymphocyte Ratio, Bleeding Risk, Nonvalvular AF.

Non-Valvuler Atriyal Fibrilasyonu Olan Hastalarda Kanama Risk Sınıflandırılmasında Platelet-Lenfosit Oranının Yeni Kullanımları: Pilot Çalışma

Öz

Amaç: Bu çalışmanın birincil amacı, PLR'nın NVAF'da kanama riskini tahmin etmedeki rolünü araştırmaktı. İkincil amaç, PLR ile tromboembolik ve kanama riski skorları arasındaki olası ilişkiyi belirlemekti. Üçüncül amaç, terapötik INR aralığındaki hastalar için PLR'nin prediktif değerini değerlendirmekti.

Yöntemler: PLR, non-valvüler AF nedeniyle warfarin tedavisi altında olan 228 hastanın tam kan sayımından hesaplandı. PLR değerlerinin ölçümünden altı ay sonra hastalara telefon edildi ve bu altı ay içinde herhangi bir kanama olayı yaşayıp yaşamadığı sorgulandı.

Bulgular: PLR hesaplandıktan sonra 48 hastada kanama olayı gözlendi. PLR ile CHA2DVAS2C (p <0.01) ve HASBLED skorları (p <0,001) arasında anlamlı bir korelasyon bulundu. ROC analizi, kesim değeri olarak 165,9 alındığında, PLR'nin kanamayı %83 hassasiyet ve %84 özgüllük ile tahmin ettiğini göstermiştir. PLR için AUC (eğrinin altındaki alan) 0,88 (p <0,001) bulundu. ROC analizinde PLR için 125,3 kesme değeri kullanıldığında, PLR %75 hassasiyetle terapötik INR aralığında bulunan hastaları öngördü ve AUC 0,73 saptandı (p <0,001). Çok değişkenli regresyon analizinde, PLR> 165,9 değeri kanama için önemli bir gösterge olarak belirlendi (p <0.001) ve 12 kattan fazla kanama riski olduğunu gösterdi (12.27, [5.74-26.21]).

Sonuç: Bu çalışmanın sonuçları PLR'nin kanama riskini saptamak için yararlı bir parametre olabileceğini göstermektedir. Bildiğimiz kadarıyla, bu PLR'nin hem CHA2DS2-VASc hem de HAS-BLED risk skorları ile korelasyonunu gösteren ilk çalışmadır. PLR ayrıca terapötik INR aralığındaki hastaları da öngörebilir.

Anahtar kelimeler: Platelet-Lenfosit Oranı, Kanama Riski, Non-Valvüler AF.

INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is one of the common heart rhythm disorders and is also associated with morbidity and mortality. It is known as an important risk factor for Ischemic Stroke (IS) and Thromboembolism (TE)[1]. Anticoagulation is the most important cornerstone in the treatment of AF. Warfarin treatment may reduce the stroke risk by 60% to 70%[2]. However, proper dosing may be hard to provide in clinical practice. Although they are highly effective treatment tools, they are also associated with significant bleeding risks. Bleeding associated with excessive anticoagulation may occur in patients receiving warfarin. The annual incidence of this complication is reported to be between 15-20%, including 1% to 3% of fatal bleeding events[3]. Adequate stratification of the risk of thromboembolism and bleeding is also mandatory. The CHA2 DS2–VASc scoring system is widely used to classify the risk of thromboembolism in AF patients. To predict the bleeding risk for individual patients, a various clinical risk estimation tools have been developed and to help distinguish which patients are at low or high risk[4]. HAS-BLED score highlight manageable risk factors to reduce the bleeding risk, has good predictive values[5].

The pathophysiology of AF is complex and not completely understood. However, inflammation

has been associated with the onset and continuity of AF and AF-related thrombosis[6,7]. Recent studies have shown that active inflammatory cells and inflammatory mediators may induce a prothrombotic state by promoting endothelial damage / dysfunction and platelet activation in AF patients, thereby linking inflammation and thrombosis[6].

Platelet-lymphocyte ratio (PLR), defined as the ratio of absolute counts of platelets and lymphocytes. PLR was introduced as an important marker for determining inflammation in cardiovascular diseases. Recently, PLR has been found to correlate positively with inflammatory markers including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 in cardiac and noncardiac patients[8,9]. PLR was also shown to be correlate positively with serum CRP level as a conventional marker for systemic inflammation[10]. The calculation of PLR is a relatively simple and inexpensive method when compared to other inflammatory cytokines.

The primary purpose of the present study was to evaluate the role of PLR to predict bleeding risk in NVAF. Secondary aim was to determine the possible relation between PLR and tromboembolic and bleeding risk scores. Tertiary aim was to investigate the predictive role of PLR in patients within the therapeutic INR range.

METHODS

Study Population

This was a single-center cohort study. A total of 228 nonvalvular AF patients who had been taking warfarin for more than 3 months and admitted to our outpatient cardiology clinic in Sakarya University Education and Research Hospital, Sakarya, Turkey for routine INR examination were included in the present study. All patients were evaluated for age, gender, DM, hypertension, stroke history, smoking status, chronic heart failure and chronic renal failure. Patients over 18 years of age who applied to the cardiology outpatient clinic and used warfarin for non-valvular AF was included to the study. Exclusion criteria included valvular heart disease, autoimmune diseases, ongoing infection or systemic inflammatory conditions, acute congestive heart failure, acute renal failure, acute coronary syndrome, acute stroke, cancer. Patients with high CRP values were also excluded. Valvular heart disease was defined as rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair, based on the definition of "non-valvular" AF in the 2014 American College of Cardiology, American Heart Association, and Heart Rhythm Society guideline[11]. Six months after the measurement of the PLR values, the patients were called and it was questioned whether they had experienced the bleeding event.

The HAS-BLED and CHA2DS2-VASc scores were calculated by examination of the medical records. AF patients were divided into two groups according to CHA2DS2-VASc thromboembolic risk scoring system; low-intermediate risk group (0 or 1) and high-risk group (≥2). AF patients also divided into two groups according to HAS-BLED bleeding risk scoring system; low- intermediate bleeding risk (score <3) and high bleeding risk (score ≥3) group.

Recent transthoracic echocardiography examinations (performed within last 2 months) were assessed for each patient from medical records. A new echocardiographic examination was performed for patients without recent echocardiographic data. Left ventricular ejection fraction (LVEF) was measured by modified Simpson's method.

This study complied with the Declaration of Helsinki, and it was approved by the independent medical ethics committee of Sakarya University Education and Research Hospital.

Laboratory Parameters

Platelet and lymphocyte counts were obtained from complete blood count. PLR was measured by dividing platelet count by lymphocyte count. The INRs and other parameters of patients were taken from medical records on hospital system.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 16.0 for Windows was used for the statistical analysis. The categorical data were expressed as percentage, and continuous data were expressed as mean ± standard deviation. Continuous variables were tested by the Kolmogorov-Smirnov test for determine normal distribution. Comparisons between groups were made using the Fisher's exact or chi-square tests for qualitative variables. The independent t-test was performed for normally distributed continuous variables and the MannWhitney U test was performed for non-normally distributed continuous variables. Correlation analyses were performed using a Spearman correlation test between parametric variables. Multivariate regression analysis was used to investigate the indicators of bleeding risk. Results of regression analysis are reported as mean (SD) and percentage or hazard ratio (HR) (95% CI). Receiver operating characteristic analysis (ROC) was used to assess the ability of the PLR to predict patients who was in the therapeutic INR range and the ideal cutoff value of PLR. A P-value of <0.05 was considered significant.

RESULTS

There was 228 patients included in the present study. Baseline demographic and laboratory characteristics of the patient group were presented in Table I.

Table I: Baseline demographic, clinical and laboratory characteristics of study group.

Age (Years)	70.25 ± 9.35
Female, [n (%)]	138 (60.5)
HT [n (%)]	144 (63.2)
DM [n (%)]	70 (30.7)
HPL [n (%)]	48 (21.1)
CVD [n (%)]	30 (13.2)
PAD [n (%)]	6 (2.6)
PE [n (%)]	5 (2.2)
Bleeding [n (%)]	48 (21.1)
PLR	147.46 ± 69.43
LVEF (%)	54.72 ± 11.36
PASP (mmHg)	28.18 ±14.32
Creatinin (mg/dl)	1.04 ± 0.27
PT	25.58 ± 10.59
aPTT	37.28 ± 9.94
INR	2.59 ± 1.61
CHA2DVAS2C	3.32 ±1.31
HASBLED	2.28 ±1.04

Note: *Data are presented as mean ± standard deviation.*

Abbreviations: *HT, Hypertension; DM, Diabetes mellitus; HPL, Hyperlipidemia; CVD, Cerebrovascular Disease; PAD, Periferic Arterial Disease; PE, Pulmonary Embolia; PLR, Platelet Lymphocite Ratio; LVEF, Left Ventricular Ejection Fraction; PASP, Pulmonary Artery Sistolic Pressure; PT, Prothrombin Time; aPTT, activated Partial Thromboplastin Time; INR, International Normalized Ratio.*

The mean age was 70.25±9.35. Female gender comprised 60.5% of the patients. In the present study mean CHA2DS2-VASc score was calculated 3.32±1.31 and mean HASBLED score was found 2.28±1.04. One hundred and seven (%47) patients was in the therapeutic INR range. The comparison of demographic, clinical and laboratory characteristics of patients with and without bleeding was presented in Table II.

Table II. The comparison of patients with and without bleeding.

Variables	Patients with bleeding (n=48)	Patients without bleeding (n=180)	*p-value*
Age, years	72.8 ± 8.8	69.5 ± 9.3	*.030*
Female, [n (%)]	31 (64.5)	107 (59.4)	.389
HT [n (%)]	34 (70.8)	110 (61.1)	.129
DM [n (%)]	12 (25.0)	58 (32.2)	.391
HPL [n (%)]	7 (14.5)	41 (22.7)	.208
CVD [n (%)]	9 (18.7)	21 (11.6)	.234
Non-steroid or ASA	5 (10.4)	18 (10.0)	.889
LVEF (%)	53.9 ± 13.3	55.0 ± 10.6	.682
Creatinin (mg/dl)	1.16 ± 0.44	1.01 ± 0.21	.111
PT	26.2 ± 9.0	25.4 ± 10.9	.610
aPTT	39.1 ± 10.3	36.7 ± 9.8	.146
INR	2.64 ± 1.20	2.57 ± 1.70	.790
CHA2DVAS2C	3.59 ± 1.24	3.25 ± 1.33	.120
HASBLED	2.85 ± 1.17	2.13 ± 0.95	*<.001*
PLR	227.8 ± 94.5	126.5 ± 40.8	*<.001*

Note: *Data presented as mean ± standard deviation.*

Abbreviations: *HT, Hypertension; DM, Diabetes Mellitus; HPL, Hyperlipidemia; CVD, Cerebrovascular Disease; ASA, Acetyl-Salicylic-Acid; LVEF, Left Ventricular Ejection Fraction; PT, Prothrombin Time; aPTT, activated Partial Thromboplastin Time; INR, International Normalized Ratio; PLR, Platelet count / Lymphocyte Ratio (/mm3).*

Bleeding was observed in fourty eight patients within 6 months after the PLR was calculated. None of the bleedings were major bleeding. Age and HAS-BLED scores were found significantly higher in the bleeding group (p: 0.03, p <0.001, respectively). Likewise, PLR was significantly higher in the bleeding group (p <0.001). There was no statistical difference between the groups in terms of concomitant non-steroid or acetyl-salicylic-acid use.

We researched correlation between PLR values and CHA2DS2-VASc and HASBLED scores and found significantly correlation between PLR and CHA2DS2-VASc (r: 0.189; p<0.01) and HASBLED score (r: 0,449; p<0.001) (Table III).

Table III. Correlation table of PLR with various factors.

	r	*p*
CHA2DVAS2C	.189	*.004*
HASBLED	.449	*<.001*
LVEF	.147	.136
CREATININ (mg/dl)	-.007	.931
INR	.089	.180

Abbreviations: *LVEF, left ventricular ejection fraction; INR, international normalized ratio.*

Significantly higher PLR values were shown in patients with high-risk CHA2DS2-VASc score group than low-moderate risk group (150.6 ± 70.3; 110.6 ± 44.5; p=0.019) (Table IV).

Table IV. The comparison of high risc CHA2DS2-VASc group with low-intermediate group.

Variables	High CHA_2DS_2-VASc group (n=210)	Low-intermediate CHA_2DS_2-VASc group (n=18)	*p-value*
Age, years	70.8 ± 9.4	63.8 ± 5.2	*<.001*
Female, [n (%)]	132 (62.9)	6 (33.3)	*.014*
HT [n (%)]	142 (67.6)	2 (11.1)	*<.001*
DM [n (%)]	70 (33.3)	0 (0.0)	*<.001*
LVEF (%)	54.6 ± 11.5	56.6 ± 2.8	.765
Creatinin (mg/dl)	1.04 ± 0.27	0.97 ± 0.29	.582
INR	2.60 ± 1.66	2.41 ± 0.57	.623
PLR	150.6 ± 70.3	110.6 ± 44.5	*.019*

Note: *Data presented as mean ± standard deviation.*

Abbreviations: *HT, Hypertension; DM, Diabetes Mellitus; LVEF, Left Ventricular Ejection Fraction; INR, International Normalized Ratio; PLR, Platelet count / Lymphocyte Ratio (/mm3).*

There was a progressive increase in PLR with respect to HASBLED scores (Figure 1).

There was also significant difference between high risk HASBLED group with low-intermediate group in terms of PLR (170.78±90.37; 132.81±46.92; p< 0.001) (Table V).

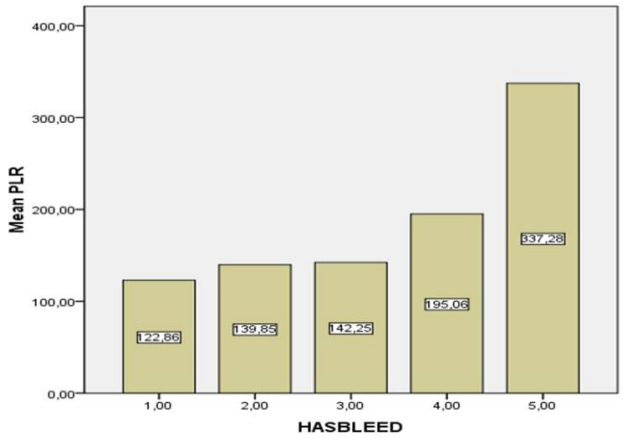

Figure 1: Relation of PLR value and HASBLED score.

Table V. The comparison of high risc HASBLED group with low-intermediate group.

Variables	High HASBLED group (n=88)	Low-intermediate HASBLED group (n=140)	*p-value*
Age	74.6 ± 7.3	67.4 ± 9.4	*<.001*
Female, [n (%)]	52 (59.1)	86 (61.4)	.727
HT [n (%)]	70 (79.5)	74 (52.9)	*<.001*
DM [n (%)]	30 (34.1)	40 (28.6)	.381
LVEF (%)	52.3 ± 13.2	56.8 ± 8.9	.051
Creatinin (mg/dl)	1.15 ± 0.35	0.96 ± 0.16	*<.001*
INR	2.74 ± 2.36	2.49 ± 0.83	.330
PLR	170.7 ± 90.3	132.8 ± 46.9	*<.001*

Note: *Data presented as mean ± standard deviation.*

Abbreviations: *HT, Hypertension; DM, Diabetes Mellitus; LVEF, Left Ventricular Ejection Fraction; INR, International Normalized Ratio; PLR, Platelet count / Lymphocyte Ratio (/mm3).*

Female patients had significantly higher PLR (160.29±73.70 vs 127.80±57.35; p< 0.001) but no difference was seen in comparison to males in terms of CHA2DS2-VASc and HASBLED risk scores.

The ROC analysis showed that PLR predicted bleeding with a sensitivity of 83% and with a specificity of 84%, using a cut-off value of 165,9. AUC (area under the curve) for PLR in ROC analysis was found 0.88 (95% CI, 0.82-0.94; p <0.001). (Figure 2).

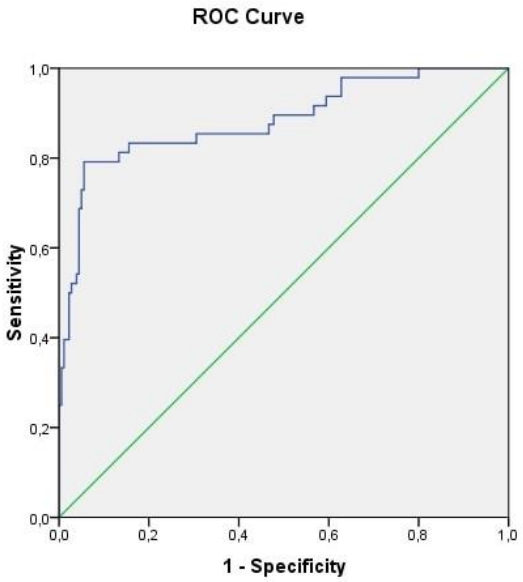

Figure 2: The sensitivity and specificity of PLR (platelet to lymphocyte ratio) for prediction of the bleeding.

In an another ROC analysis, PLR predicted the patients in therapeutic INR range with a sensitivity of 75% and with a specificity of 62%, using a cut-off value of 125,3. The AUC for the PLR was found 0.73 (95% CI, 0.66-0.79; p< 0.001) (Figure 3).

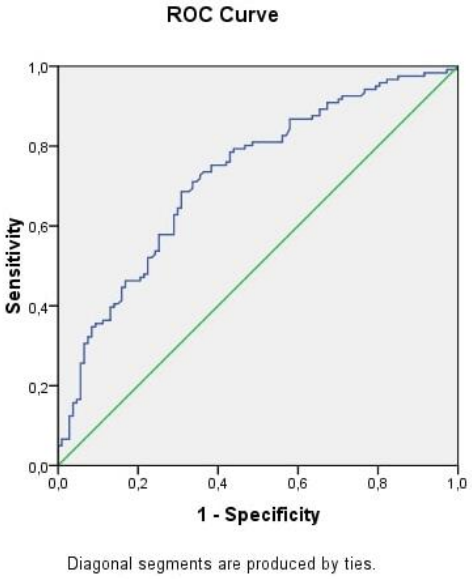

Figure 3: The sensitivity and specificity of PLR (platelet to lymphocyte ratio) for prediction of the INR in therapeutic range.

On multivariate regression analysis (reported as HR [95% CI]), significant indicator for bleeding was PLR (p<0.001). Patients with PLR>165,9 had more than a 12-fold increased risk of bleeding (12.27, [5.74-26.21]). It was also found that low-intermediate HASBLED group had 45% lower risk than high HASBLED risk group for developing bleeding event (0.55 [95% CI, 0.31-0.99] (p=0.04).

DISCUSSION

This study consists of NVAF patients who were admitted to the cardiology outpatient clinic and receiving warfarin. The results revealed that PLR is a significant indicator for bleeding in patients with NVAH. This study demonstrate that there is a significant correlation between the PLR with bleeding and thromboembolic risk scores. The PLR is a predictive indicator of patients within the therapeutic INR range.

NVAF is the most common sustained arrhythmia with high prevalence, especially in the elderly population[1]. NVAF is associated with significant morbidity and mortality, particularly due to thromboembolism and stroke[5]. The underlying pathophysiology of NVAF is complex and not fully resolved. The previous studies have established a strong relationship between atrial fibrillation and inflammation. One of the inflammatory pathways underlying AF is leukocyte activation[12]. Also activated platelets precipitate to produce inflammatory substances from endothelial cells and leukocytes that cause monocyte adhesion and transmigration and thereby enhancing the inflammatory process[13,14]. In previous studies, major adverse cardiovascular outcomes were associated with higher platelets and lower lymphocyte counts. Gary et al. reported that higher platelet volume may change blood viscosity and increase inflammation[15]. Davi et al. concluded that higher platelet activity was associated with higher rates of cardiovascular events[16]. Furthermore, platelet counts were found to be associated with short and long term mortality in patients with ST-elevated and non-ST elevated MI and unstable angina pectoris[17,18]. It was also documented that fibrinogen levels and platelet counts are correlated positively and associated to inflammation in acute coronary syndrome patients.

Several studies have investigated the association of PLR with bleeding in various diseases. Zou et al reported that PLR was associated with gastrointestinal hemorrhage in patients with acute cerebral haemorrhage[19]. In an another study, the mean PLR value of the pediatric recurrent epistaxis group was statistically higher than the control group[20]. In the study carried out by Gayret et al, PLR of the patients with gastrointestinal bleeding were found to be significantly increased compared to those without bleeding[21]. On the other hand, there are only few clinical trials demonstrating an association between PLR and atrial fibrillation, but none of them is related to bleeding. Saskın et al. revealed that the preoperative high platelet to lymphocyte ratio was independent risk factor for occurrence of atrial fibrillation in the postoperative early period[22]. In patients with paroxysmal atrial fibrillation, a higher PLR has been documented to be significantly associated with the presence of silent brain infarction (SBI). On the contrary, no significant relationship was found between CHA2DS2-VASc scores and presence of SBI in this study[23].

Determining of risk factors for bleeding complications in warfarin patients would allow identification of patients at risk. In the present study; age, drugs with concomitant use that interfere with haemostasis (aspirin or non-steroidal anti-inflammatory drugs), HASBLED score and PLR were significantly higher in bleeding group while they are receiving warfarin treatment. In previous studies, bleeding rates were found different in patients receiving warfarin treatment depending on the

characteristics of the study group. Monteiro et al found that the annual incidence of minor bleeding was 17.7%[24]. Oztürk et al reported that 33.3% of the patients had experienced minor and/or major bleeding at least once during 1-year period, moreover bleeding complications detected in 38.9% of patients ≥ 65 years of age and in 26.2% of patients <65 years of age[25]. A recent study showed that the clinically relevant minor bleeds and severe bleeding events were found 66.7% in the warfarin treatment group during the two-year follow-up[26]. In the present study, minor bleeding rate was found 21.1%. The association of PLR with bleeding was investigated for the first time in this study, and it was shown that PLR is an independent risk factor for minor bleeding.

Our study revealed that CHA2DS2-VASc score was positively correlated with PLR. This finding suggests that PLR might be associated with the thromboembolic risk exhibited by CHA2DS2-VASc score in patients with nonvalvular AF[27]. At the same time in our study higher PLR was found to be associated with a high CHA2DS2-VASc score. In accordance with these findings, our study also showed a significant positive correlation between PLR and HASBLED score. Increased PLR levels consistent with the gradual increase in the HASBLED score suggest that PLR may have a predictive role for bleeding risk. The association between PLR and CHA2DS2-VASc and HASBLED scores was determined for the first time with our study. The detection of bleeding events with high sensitivity and specificity by the PLR is another important finding in this study. In addition, PLR values above 165.9 were associated with more than 12-fold increased risk of bleeding.

INR values lower than 2.0 contribute to the increased risk of embolic stroke, whereas high INR values greater than 3.0 contribute to the increased risk of bleeding. In the present study we found that PLR may predict the INR value in the therapeutic range with 75% sensitivity. This result can be explained as high PLR value may contribute to prediction of increased risk of stroke and bleeding. In our study, correlations of the PLR with CHA2DS2-VASc and HASBLED risk scores may also support this result.

Female gender is one of the paramater of CHA2DS2-VASc score. In the present study although female gender's CHA2DS2-VASc and HASBLED scores were not different from men, PLR was found to be significantly higher in female gender. Depending on this result, it may be suggested that females may have more risk for stroke and bleeding than men.

CONCLUSION

The results of the present study indicates that, PLR is important variable for determining patient's minor bleeding complications while they are receiving anticoagulation treatment. INR needs to be more closely monitored among patients whose PLR>165,9 on warfarin treatment. To our knowledge, this is the first study to demonstrate a correlation between PLR and CHA2DS2-VASc and HASBLED risk scores. PLR has been found to be closely related to both scoring systems, therefore we suggest that PLR may be used as a simple and inexpensive adjunct to CHAD2S2-VASc and HASBLED scores to predict thromboembolic and bleeding risks. PLR may also be useful to predict the patients within the therapeutic INR range. These results are encouraging regarding the use of the PLR in risk prediction in NVAF as an inexpensive, readily available, and practical parameter. Other large-scale, randomized studies are needed to clarify the role of the PLR in the pathophysiology of NVAF.

LIMITATIONS

The primary limitation of the present study is retrospective design. Furthermore, current study is based on a single-center experience and the sample size was relatively small. Moreover, other inflammatory markers such as TNF-α,

high-sensitivity CRP, interleukins and chemokines were not addressed in this study.

FOOTNOTES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Committee Approval: This study complied with the Declaration of Helsinki, and it was approved by the independent medical ethics committee of Sakarya University Education and Research Hospital.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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