Received: 24 August 2017 | Revised: 23 November 2017 | Accepted: 7 December 2017

DOI: 10.1002/clc.22869

WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Use of neutrophil-lymphocyte ratio for risk stratification and relationship with time in therapeutic range in patients with nonvalvular atrial fibrillation: A pilot study

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Background: Atrial fibrillation is one of the most common abnormal heart rhythms. Neutrophil-lymphocyte ratio (NLR) has emerged as a potential marker for the level of inflammation in cardiac disorders.

Hypothesis: NLR might be associated with thrombosis and bleeding risk scores and might predict cardioembolic risk in nonvalvular atrial fibrillation (NVAF) patients within the therapeutic international normalized ratio (INR).

Methods: We enrolled 272 patients taking warfarin for NVAF and classified them into 2 groups: Group A consisted of patients (n = 132) whose time in therapeutic range (TTR) was ≥65%, and Group B comprised patients (n = 139) whose TTR was <65%.

Results: NLR values were higher in group B than in group A ($P < 0.0001$). Patients classified as high risk according to CHA_2DS_2-VASc score had significantly higher NLR levels ($P = 0.002$) than those classified as low and intermediate risk. Furthermore, NLR levels were significantly correlated with CHA_2DS_2-VASc and HAS-BLED scores ($P < 0.001$ and $P < 0.0001$, respectively). NLR predicted patients within therapeutic INR range (TTR ≥65%) with sensitivity of 81% and specificity of 71% in a receiver operator characteristic curve analysis, using a cutoff value of 2.17. Area under the curve for NLR was 0.81 ($P < 0.0001$).

Conclusions: To our knowledge, this is the first study showing correlation of NLR with both CHA_2DS_2-VASc and HAS-BLED risk scores. NLR might represent a useful marker to identify patients with high risks of stroke and bleeding and may have predictive value in identifying patients within the therapeutic INR range.

KEYWORDS

Atrial Fibrillation, Bleeding, Neutrophil-Lymphocyte Ratio, Stroke, Time in Therapeutic Range

1 | INTRODUCTION

Atrial fibrillation (AF) is the most frequently sustained arrhythmia in clinical practice.[1] AF is associated with significant morbidity and mortality, and it is a major risk factor for thromboembolic events and death from all causes.[2] Numerous scoring systems have been proposed to predict thromboembolism risk in AF patients. Among these, the CHA_2DS_2-VASc score is currently the recommended clinical risk-prediction tool to evaluate the thromboembolism risk in patients with nonvalvular atrial fibrillation (NVAF).[3] The HAS-BLED score is the most widely preferred method for the prediction of bleeding risk.[4]

Warfarin, a vitamin K antagonist, is prescribed to many patients to combat the risk of thromboembolism. In such patients, routine follow-up is required at regular intervals to achieve target international normalized ratio (INR) values. However, achieving and maintaining the target INR range remains a problem of warfarin treatment. The risk of thromboembolism increases in patients with an INR value below the target INR range, and the risk of bleeding increases in those who exceed the target INR range. The most feasible method for quantitative assessments of the therapeutic effectiveness of vitamin K antagonists over time is measurement of the percentage of time in therapeutic range (TTR). TTR has been shown to correlate strongly with the clinical outcomes of hemorrhage or thrombosis

and to be a reliable measure of the quality of anticoagulation management.[5]

Current evidence reveales that the pathophysiology of AF is multifactorial. Recent studies showed that inflammation playes a key role in the initiation, maintenance, and recurrence of AF.[6,7] The neutrophil-lymphocyte ratio (NLR) is a simple, inexpensive, and widely available biomarker. It has been shown that NLR is also a marker of inflammation.[8] Thus, NLR might serve as an effective predictor of outcomes in AF.[9]

The primary aim of this study was to investigate the role of NLR in predicting thrombosis or bleeding risk scores in patients with NVAF. A secondary aim was to evaluate the predictive value of NLR for cardioembolic risk in NVAF patients in the therapeutic INR range.

2 | METHODS

2.1 | Study population

This was a retrospective single-center study based on medical records. In total, 271 NVAF patients admitted to our outpatient cardiology clinic for routine INR examinations were enrolled in this study. All the patients had taken warfarin for >3 months. Previous research showed that the percentage of time that patients taking warfarin had an INR of 2.0 to 3.0 within the target value (ie, TTR) was important for the safety and effectiveness of warfarin anticoagulation and suggested that a TTR of >65% indicated good control.[5] Therefore, in the present study, the patients were divided into 2 groups: those with a TTR ≥65% and those with a TTR <65%.

All the patients were screened for the presence of cardiovascular (CV) risk factors, such as hypertension, diabetes mellitus, stroke history, sex, age, and chronic renal failure. The inclusion criteria were NVAF patients age > 18 years who presented to the cardiology outpatient clinic and had used warfarin for >3 months. The exclusion criteria included autoimmune disease, clinically significant valvular heart disease, acute coronary syndrome, acute renal failure, acute heart failure, acute stroke, cancer, ongoing infection, or systemic inflammatory conditions. Patients with high C-reactive protein values (>3 mg/L) were also excluded. The medical history and clinical features of the patients were recorded. This study was approved by the local institutional ethics committee.

2.2 | Measurement instruments and laboratory parameters

The CHA_2DS_2-VASc[10] scoring system was used to stratify the risk of long-term thromboembolic events related to AF, and the HAS-BLED score[4] was used to determine bleeding risk. The patients were also classified into different risk groups according to the CHA_2DS_2-VASc thromboembolic risk score and HAS-BLED bleeding risk score, as follows: a low-intermediate thromboembolic risk group (score 0 or 1), high thromboembolic risk group (score ≥ 2), low-intermediate bleeding risk group (score < 3), and high bleeding risk group (score ≥ 3). Blood samples were collected from the antecubital vein using a 21-gauge sterile syringe in the laboratory. Neutrophils and lymphocytes were obtained from a complete blood count. The NLR was calculated based on the ratio of absolute counts of neutrophils and lymphocytes.

2.3 | Calculation of TTR

The INRs of patients were obtained from their outpatient clinic medical reports, where every patient had ≥3 INR measurements. TTR was calculated according to F.R. Rosendaal's algorithm.[11]

2.4 | Statistical analysis

All statistical data were analyzed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL). Continuous data are expressed as mean ± SD, and the categorical data are expressed as percentages. Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Comparisons between groups were performed using the χ^2 or Fisher exact test for qualitative variables when appropriate, the independent *t* test for normally distributed continuous variables, and the Mann–Whitney *U* test for non–normally distributed continuous variables. The Pearson test was used in the correlation analysis between parametric variables. To determine the ideal cutoff value of the NLR, a receiver operating characteristic (ROC) curve was used. A *P* value <0.05 was considered significant.

3 | RESULTS

The study population included 107 men and 164 women, with a mean age of 70.25 ± 9.35 years. Group A included 132 patients with TTR ≥65%, and Group B comprised 139 patients with TTR <65%. Baseline demographic, clinical, and laboratory characteristics of the 2 groups are presented in Table 1. There were no differences in baseline clinical characteristics of the groups, such as age, sex, hypertension, diabetes mellitus, heart failure, vascular disease, and a previous history of stroke ($P > 0.05$).

Each group was compared according to NLR values, CHA_2DS_2-VASc scores, and HAS-BLED scores (Table 2). The NLR was significantly higher in group B as compared with that in group A ($P < 0.0001$). CHA_2DS_2-VASc and HAS-BLED scores were also higher in group B than in Group A ($P = 0.028$ and $P < 0.0001$, respectively).

When the low-intermediate and high-risk CHA_2DS_2-VASc score groups were compared with the NLRs of the groups, the NLR of the high-risk group was significantly higher than that of the low-intermediate risk group (2.64 ± 1.26 vs 1.97 ± 0.76; $P = 0.002$). However, there was no significant difference between low-intermediate and high HAS-BLED score groups (2.49 ± 1.28 vs 2.78 ± 1.15; $P = 0.084$). Furthermore the NLR showed a significant correlation with CHA_2DS_2-VASc and HAS-BLED scores ($P < 0.001$, $r = 0.205$; and $P < 0.0001$, $r = 0.228$, respectively).

The ROC analysis showed that NLR predicted TTR (≥65%) with 81% sensitivity and 71% specificity, using a cutoff value of 2.17 (ROC area: 0.812, 95% confidence interval: 0.76-0.86, $P < 0.0001$). Using a cutoff value of 1.70, the sensitivity increased to 90%. The ROC curve of the NLR is shown in the Figure 1.

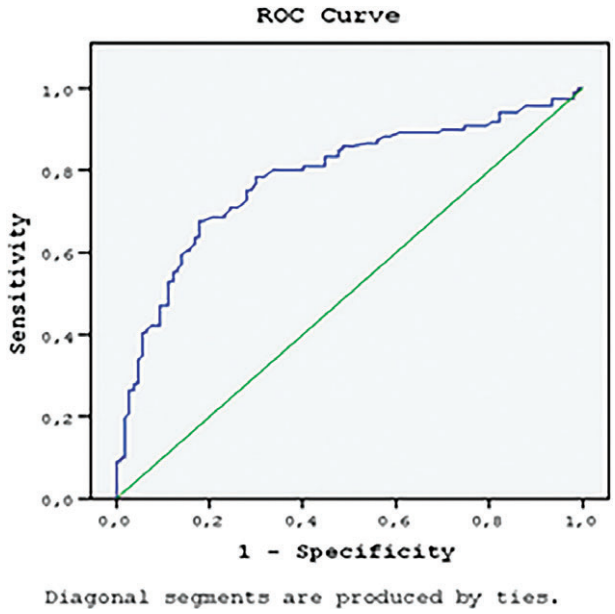

FIGURE 1 The ROC curve analysis of NLR for predicting the TTR ≥65%. Abbreviations: NLR, neutrophil-lymphocyte ratio; ROC, receiver operating characteristic; TTR, time in therapeutic range

4 | DISCUSSION

The present study consisted of patients admitted to the cardiology outpatient clinic who used warfarin and had a diagnosis of NVAF. The results revealed a correlation between NLR and thromboembolic and bleeding risk scores. The NLR was a predictive marker of patients within the therapeutic INR range.

The NLR is a novel parameter, investigated in conditions with inflammatory pathogenesis, and has been widely studied in CV diseases.[12] It was reported to be a strong predictor of adverse CV outcome.[13] Previous studies also demonstrated that NLR was associated with inflammation and thrombogenicity.[14,15] Furthermore, a high preoperative NLR was related to an increased incidence of AF in coronary artery bypass grafting patients after surgery.[16] In a study of a patient population with diabetes, the NLR was significantly higher in an AF group than an AF-free group, and it was an independent risk factor for AF.[17] A similar study found that NLR was higher in persistent/permanent NVAF patients than in cases of paroxysmal AF.[18]

A previous study of AF patients detected a history of strokes, transient ischemic attacks, or systemic thromboembolisms in 16% of all patients, in addition to a history of bleeding in 14% of patients.[19] In a study of patients with NVAF, a high NLR was an independent risk factor for the presence of a left atrial thrombus on transesophageal echocardiography.[14] A large retrospective cohort showed that each increase in NLR quartile was associated with a significant increment in the risk of strokes and that adding the NLR to the CHA_2DS_2-VASc risk score improved the accuracy of stroke prediction.[20] NLR has been shown to increase the risk of thromboembolic stroke in patients with NVAF.[9] In the same study, the mean NLR of stroke patients was significantly higher than that of nonstroke patients. Akdag et al. revealed that the NLR was correlated with the CHA_2DS_2-VASc score in patients with NVAF, which was an independent predictor of a high CHA_2DS_2-VASc score.[21] In the present study, the NLR was higher in the high CHA_2DS_2-VASc group, and the NLR was correlated with the CHA_2DS_2-VASc score, in accordance with the findings of a previous study. In addition, this study revealed a significant correlation between NLR and HAS-BLED score. The CHA_2DS_2-VASc score was higher in group B (TTR <65%). The results of the present study indicate that the NLR might be a useful parameter to detect the risk of thromboembolism and bleeding.

TABLE 1 Baseline demographic, clinical, and laboratory characteristics of groups A and B

	Group A, TTR ≥65%, n = 132	Group B, TTR <65%, n = 139	*P* Value
Age, y	69.11 ± 8.87	70.97 ± 9.26	0.092
Female sex	76 (58)	82 (59)	0.813
Cr, mg/dL	1.03 ± 0.19	1.05 ± 0.32	0.627
HTN	83 (63)	87 (63)	0.941
DM	40 (30)	40 (29)	0.783
Hyperlipidemia	33 (25)	26 (19)	0.209
Stroke	12 (9)	20 (15)	0.130
COPD	23 (17)	35 (25)	0.120

Abbreviations: COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; HTN, hypertension; SD, standard deviation; TTR, time in therapeutic range. Data are presented as n (%) or mean ± SD.

TABLE 2 Comparison of groups with respect to NLR, CHA_2DS_2-VASc, and HAS-BLED scores with independent *t* test

Score	Group A	Group B	*P* Value
NLR	1.94 ± 0.71	3.21 ± 1.58	<0.0001
CHA_2DS_2-VASc	3.12 ± 1.32	3.48 ± 1.33	<0.05
HAS-BLED	1.80 ± 0.74	2.58 ± 0.98	<0.0001

Abbreviations: CHA_2DS_2-VASc, congestive HF, HTN, age ≥ 75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (female); DM, diabetes mellitus; HAS-BLED, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly age > 65 years; HF, heart failure; HTN, hypertension; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; SD, standard deviation; TIA, transient ischemic attack. Data are presented as mean ± SD.

4.1 | Study limitations

The retrospective design is the main limitation of this study. Moreover, this study was based on single-center experiments. Another limitation of this study was the relatively small sample size.

5 | CONCLUSION

Risk stratification is essential to determine thromboembolic and bleeding risk in patients with NVAF. The NLR, which can be measured by an inexpensive and simple method, might represent a useful marker to identify patients with high thromboembolic and bleeding risk in patients with NVAF. To our knowledge, this is the first study to demonstrate a correlation of NLR with the CHA_2DS_2-VASc and HAS-BLED risk scores. The NLR was strongly associated with both scoring systems. Therefore, we suggest that NLR can be used as a

simple and inexpensive adjunct to CHA_2DS_2-VASc and HAS-BLED scores to predict thromboembolic and bleeding risk. The NLR may also be helpful to identify patients within the therapeutic INR range. Further studies with larger sample sizes are needed to elucidate the role of the NLR as an additional risk-stratification tool in patients with NVAF.

Conflicts of interest

The authors declare no potential conflicts of interest.

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How to cite this article: Cosansu K, Vatan MB, Gunduz H, Akdemir R. Use of neutrophil-lymphocyte ratio for risk stratification and relationship with time in therapeutic range in patients with nonvalvular atrial fibrillation: A pilot study. *Clin Cardiol*. 2018;41:339–342. https://doi.org/10.1002/clc.22869