INTRODUCTION

Atrial fibrillation (AF) is the most common clinical cardiac arrhythmia in the general population and increases the risk of cardiovascular morbidity and mortality. The prevalence of AF gradually increases owing to ageing of the population. Diabetes mellitus (DM) is a significant risk factor for the development and progression of AF as well as hypertension, and atherosclerosis. There are several possible pathways to the mechanisms of AF associated with DM; long-term inflammation is one and probably the most common. Previous two studies showed the higher levels of C-reactive protein (CRP), and other inflammatory markers have been monitored in atrial biopsies of diabetic patients with AF.

Neutrophil to lymphocyte ratio (NLR) is an inflammatory marker recently introduced and used in many studies, which is both simple and of low cost. NLR, which can be derived from the white blood cell (WBC) count, is a novel marker of prognosis in patients with cardiovascular disease. While high neutrophil counts indicate inflammation, low lymphocyte counts reflect poor general health and physiologic stress. NLR combines these two independent markers of inflammation. In a recent study, increased NLR has been shown to be related to AF development after cardiac surgery.

To our knowledge, there is not a study that consistent evidence about the link between NLR and AF in DM. In the study, we aimed to investigate the possible association of chronic AF with NLR in patients who have type 2 DM.
Methods

Patients

The study design is retrospective cohort study. Ethical approval for the study was obtained from the local ethics committee. A total of 812 DM patients, diagnosed according to the American Diabetes Association criteria\(^{(10)}\), were retrospectively screened between March 2012 and March 2013 in three different University Hospital. Subjects in all groups with a cardiac rhythm other than AF or NSR, acute coronary syndromes, valvular or dilated heart diseases, acute or chronic infectious diseases (urinary tract infection, pneumonia etc.), uncontrolled hypertension, cerebrovascular diseases, thrombosis, malignancies, thyroid disorders, pregnancy, hematological disorders, and liver or renal insufficiency were excluded from the study. Remaining 144 patients with DM and a history of electrocardiographic documented persistent AF were assigned to the AF group (Group 1) (n=72) and, if no history of AF was evident, patients were placed in the normal sinus rhythm (NSR) group (Group 2) (n=72).

Hypertension was diagnosed on the basis of JNC-VII criteria\(^{(11)}\). Smoking status was classified as current smoker or non-smoker. Medical record review provided information on clinical characteristics including duration of DM and AF, diabetic retinopathy, height, weight, valvular heart disease, coronary artery disease (CAD), and cerebrovascular accidents. Additionally, current drugs received by patients were also assessed. Body mass index (BMI) was calculated as weight/length\(^2\) (kg/m\(^2\)).

Laboratory measurements

The WBC, neutrophil, and lymphocyte count, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, hemoglobin A1c (HbA1c), and microalbuminuria were retrospectively recorded from patient files. Baseline NLR was measured by dividing neutrophil count to lymphocyte count. These whole blood samples were then analyzed within one hour of venipuncture on an automated blood cell counter. WBC counts more than 12.0 (x 10^3 cells/ mm^3) and less than 4.0 (x 10^3 cells/ mm^3) were exclusion criteria for the study. Microalbuminuria was defined as an albumin excretion of 30-299 mg/24 hours.

Statistical analysis

The statistical analyses were performed using software (SPSS 18.0). Parametric values were given as mean±standard deviation, and non-parametric values were given as a percentage. To compare parametric continuous variables, Student’s t-test was used; to compare nonparametric continuous variables, the Mann–Whitney U-test was used. Categorical data were compared by Chi-square distribution. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of NLR and CRP (at which sensitivity and specificity would be maximal) for the prediction of AF. Variables found to be statistically significant in univariate analyses were entered into multivariate logistic regression analysis. Multivariate logistic regression models were created to identify independent predictors of AF. Two-tailed P-values of less than 0.05 were considered to indicate statistical significance.

Results

There were no significant differences among patients with or without atrial fibrillation in terms of gender, age, microalbuminuria, retinopathy, CAD, thyroid disorder, mean platelet volume (MPV), WBC, BMI, smoking, hypertension, duration of DM, LDL, HDL, triglyceride, uric acid (Table 1). The mean age of the study population was 65.01±9.32 (Group 1) and 64.72±8.92 (Group 2) years. HbA1c level was higher in AF group compared to NSR group (8.73±0.68 vs. 8.49±0.69, \(p<0.05\)).

NLR was different among patients with atrial fibrillation and without atrial fibrillation (2.87±1.3 vs. 2.2±1.56 \(p=0.019\)) (Table 1). CRP level was higher in Group 1 compared to Group 2 (2.97±0.81 vs. 2.09±1.01, \(p<0.001\)). Variables found to be statistically significant in univariate analyses were entered into multivariate logistic regression analysis. Multivariate logistic regression analysis showed that NLR and CRP were only independently risk factor associated with AF (Odds ratio of N/L: 3.486, %CI: 1.491-8.151, \(p=0.004\) and odds ratio of CRP: 2.620, %CI: 1.260-5.448, \(p=0.01\) respectively) (Table 2). ROC-curve analyses were applied to determine the cut-off point of CRP and NLR (Figure 1). Cut-off point of NLR was at 2.38, and sensitivity, specificity was 75.7% and 67% respectively. Cut-off point of CRP was at 2.45, and sensitivity and specificity was 70.3% and 53.6% respectively.
The results of our study demonstrated that NLR was significantly higher in diabetic patients with AF than in diabetic patients with NSR. High levels of NLR were independently associated with the presence of AF in patients with type 2 DM. Besides, we found that NLR value of 2.38 had 75.7% sensitivity and 67% specificity for prediction of AF development in patients with DM.

Many mechanisms may play a role to the relationship between diabetes and atrial fibrillation. The suggested mechanisms include autonomic remodeling, structural remodeling, electrical remodeling, and insulin resistance(3). Inflammation of diabetes-related may play a potential role in the pathogenesis of atrial remodeling. Diabetic patients have higher levels of C-reactive protein which may support myocardial fibrosis and diastolic dysfunction(12, 13).

**Table 1**: Basal characteristics of patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>%CI</td>
</tr>
<tr>
<td>NLR</td>
<td>1.462</td>
<td>1.047-2.057</td>
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<tr>
<td>CRP</td>
<td>2.650</td>
<td>1.444-4.864</td>
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<tr>
<td>HbA1c</td>
<td>1.675</td>
<td>0.994-2.825</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.933</td>
<td>0.642-3.403</td>
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<tr>
<td>WBC</td>
<td>0.955</td>
<td>0.809-1.129</td>
</tr>
<tr>
<td>MPV</td>
<td>1.242</td>
<td>0.941-1.639</td>
</tr>
<tr>
<td>Age</td>
<td>1.118</td>
<td>1.066-1.173</td>
</tr>
<tr>
<td>Sex(male)</td>
<td>1.755</td>
<td>0.863-3.570</td>
</tr>
<tr>
<td>CAD</td>
<td>0.991</td>
<td>0.986-1.997</td>
</tr>
<tr>
<td>HT</td>
<td>0.677</td>
<td>0.088-5.193</td>
</tr>
<tr>
<td>LDL</td>
<td>0.994</td>
<td>0.988-1.005</td>
</tr>
<tr>
<td>DM duration</td>
<td>1.027</td>
<td>0.982-1.074</td>
</tr>
<tr>
<td>BMI</td>
<td>1.012</td>
<td>0.943-1.085</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.712</td>
<td>0.703-1.012</td>
</tr>
</tbody>
</table>

**Discussion**

The results of our study demonstrated that NLR was significantly higher in diabetic patients with AF than in diabetic patients with NSR. High levels of NLR were independently associated with the presence of AF in patients with type 2 DM. Besides, we found that NLR value of 2.38 had 75.7% sensitivity and 67% specificity for prediction of AF development in patients with DM.

Many mechanisms may play a role to the relationship between diabetes and atrial fibrillation. The suggested mechanisms include autonomic remodeling, structural remodeling, electrical remodeling, and insulin resistance(3). Inflammation of diabetes-related may play a potential role in the pathogenesis of atrial remodeling. Diabetic patients have higher levels of C-reactive protein which may support myocardial fibrosis and diastolic dysfunction(12, 13).
Chatterjee et al. suggested that inflammation cause diminishing of cell survival pathways and increasing oxidative stress. These changes cause faster apoptosis and myocardial necrosis forming a ‘substrate’/scar tissue and consequently lead to arrhythmias\(^{(14)}\). It is known that neutrophils secrete may be associated with the acute inflammatory response to tissue injury. While high neutrophil counts indicate inflammation, low lymphocyte counts reflect poor general health and physiologic stress. NLR combines the predictive power of both increased neutrophil count and decreased lymphocyte count\(^{(6)}\).

NRL has been gaining attention as a significant indicator of inflammation in recent years. Elevated levels of NRL were also found associated with poor survival of patients with cardiovascular disease\(^{(8, 15, 16)}\). Many cancer survival studies have suggested that NRL is a significant predictor of overall and disease specific survival of patients\(^{(17, 18)}\).

In a recent retrospective study, the relationship of ventricular arrhythmias developing during percutaneous coronary interventions to inflammatory markers like WBC count and NRL was shown\(^{(14)}\).

In a recent study, Gibson et al.\(^{(9)}\) found that both preoperative and postoperative elevations in NRL were related to AF development after coronary artery bypass surgery. However, there was no correlation between AF development and other WBC parameters or CRP values. In another study, Canpolat et al.\(^{(10)}\) have demonstrated that the NRL is a powerful and independent predictor of AF recurrence in patients undergoing successful cryoablation. Present study demonstrated relationship between AF and NRL and this finding was consistent with previous studies. On the contrary, Aribas et al.\(^{(20)}\) did not reveal a association between NRL and AF recurrence after successful cardioversion. These studies which revealed association between AF and NRL confirm present study. There is a need of a new marker to indicate this relationship. In present study, NRL had a higher sensitivity and specificity. NRL may be useful marker to indicate presence or developing of atrial fibrillation.

Many epidemiological studies have identified a strong link between diabetes and AF\(^{(21-23)}\). Turgut et al.\(^{(24)}\) indicated that diabetic patients with AF had significantly higher MPV values than did diabetic patients with NSR. In our study, there were no significant differences between AF and NSR in MPV values. MPV is strongly affected by inflammation, coronary artery disease, hypertension, cerebrovascular disease, hyperlipidemia. It must be taken to and studied very fast in one hour after venipuncture to assessment reliably\(^{(25)}\).

In present study, we showed that NRL was increased in diabetic patients with AF when compared to diabetic patients with NSR. NRL could be an important measure of systemic inflammation as it is cost effective, readily available. Increased NRL may be independent marker of atrial fibrillation in diabetic patients.

**Conclusion**

Our study concluded that NRL is an useful predictor of AF in diabetic patients. With this result, we thought that the NRL will become a novel target for the prevention of AF in diabetic patient together with in future different prospective studies.

**Limitations**

There are several limitations of our study. First, because of its retrospective design, the causal relationship between NRL and AF in type 2 DM cannot be completely established. Second, results were dependent on single measurements which could not rule out the laboratory measurement errors and further prospective studies are required to support our results.

**References**


5) A. Frustaci CC, F. Bellocci, E. Morgante, M.A. Russo, A. Maseri. Histological substrate of atrial
Neutrophil to lymphocyte ratio is a useful predictor of atrial fibrillation in patients with diabetes mellitus.


