NEUTROPHIL TO LYMPHOCYTE RATIO IS A USEFUL PREDICTOR OF ATRIAL FIBRILLATION IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Background & aims*: Diabetes mellitus is an important risk factor for the development and progression of atrial fibrillation. There are several possible pathways to the mechanisms of atrial fibrillation associated with diabetes mellitus. Long-term inflammation is one of the mechanisms. To our knowledge, there is not a study that consistent evidence about the link between atrial fibrillation and neutrophil to lymphocyte ratio in diabetes mellitus. In the study, we aimed to investigate the possible association of chronic atrial fibrillation with neutrophil to lymphocyte ratio in patients who have type 2 diabetes mellitus.*

Methods*: A total of 812 diabetes mellitus patients were retrospectively screened between March 2012 and March 2013. Patients with diabetes mellitus and a history of electrocardiographically documented persistent atrial fibrillation were assigned to the atrial fibrillation group (Group 1) (n=72) and, if no history of atrial fibrillation was evident, patients were placed in the normal sinus rhythm group (Group 2) (n=72).*

Results*: Neutrophil to lymphocyte ratio was different among patients with atrial fibrillation and without atrial fibrillation (2.87±1.3 vs. 2.2±1.56 p=0.019). Cut-off point of Neutrophil to lymphocyte ratio was at 2.38, and sensitivity, specificity was 75.7% and 67% respectively*

Conclusions*: In conclusion, we suggest that neutrophil/lymphocyte ratio increase in diabetic patients with atrial fibrillation when compared to diabetic patients without atrial fibrillation. We think that neutrophil to lymphocyte ratio can be used as a marker of development of atrial fibrillation in diabetic patients.*

Key words*: Diabetes mellitus, atrial fibrillation, neutrophil to lymphocyte ratio, inflammation.*

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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[1]. Diabetes mellitus (DM) is a significant risk factor for the development and progression of AF as well as hypertension, and atherosclerosis[2]. There are several possible pathways to the mechanisms of AF associated with DM; long-term inflammation is one and probably the most common[3]. 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[4, 5].

Neutrophil to lymphocyte ratio (NLR) is an inflammatory marker recently introduced and used in many studies, which is both simple and of low cost[6]. NLR, which can be derived from the white blood cell (WBC) count, is a novel marker of prognosis in patients with cardiovascular disease[7, 8]. While high neutrophil counts indicate inflammation, low lymphocyte counts reflect poor general health and physiologic stress. NLR combines these two independent markers of inflammation[6] In a recent study, increased NLR has been shown to be related to AF development after cardiac surgery[9].

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/length2 (kg/m2).

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 103 cells/ mm3) and less than 4.0 (x 103 cells/ mm3) 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.

	Group 1 n=72	Group 2 n=72	p
Age	65.01±9.32	64.72±8.92	0.218
Sex(male) %	48.2	51.3	0.908
BMI (kg/m2)	32.6±6.4	31.5±7.2	0.848
HT %	69	64	0.721
Smoking %	43	46	0.238
DM duration (years)	10.01±1.21	9.8±1.3	0.224
CAD %	44	51	0.456
Microalbuminuria %	41	32	0.074
Retinopathy %	32	29	0.232
TG mg/dL	153.87±61.76	165.28±60.42	0.118
HDL mg/dL	43.57±14.18	40.86±12.19	0.441
LDL mg/dL	134.29±38.94	114.21±35.3	0.124
Creatinine mg/dL	0.904±1.31	0.95±1.33	0.767
Glucose mg/dL	132.12±71.49	133.03±72.11	0.400
HbA1c %	8.73±0.68	8.49±0.69	0.048
Uric acid mg/dL	6.28±2.54	5.27±0.94	0.110
CRP mg/L	2.97±0.81	2.09±1.01	0.001
WBC /mm3	7.86±2.04	7.67±2.03	0.594
NLR	2.87±1.3	2.2±1.56	0.019
MPV fL	8.31±1.12	7.99±1.39	0.125

Table 1: Basal characteristics of patients.
NLR: Neutrophil lymphocyte ratio, MPV: Mean platelet volume, WBC: White blood cell, BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG:Triglyceride, CRP: C reactive protein, HT:Hypertension, DM:Diabetes mellitus, CAD: Coronary artery disease
Data are presented as mean±standard deviation.

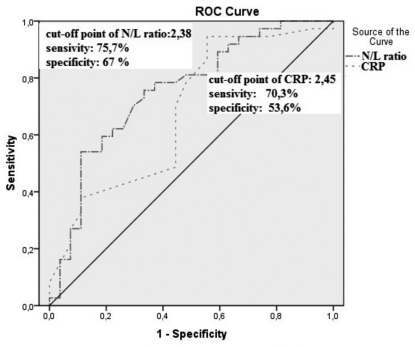

Figure 1: ROC curve comparing sensitivity and specificity of CRP and NLR.

Variables	Univariate			Multivariate		
	OR	%CI	p	OR	%CI	p
NLR	1.462	1.047-2.057	0.029	3.486	1.491-8.151	0.004
CRP	2.650	1.444-4.864	0.002	2.620	1.260-5.448	0.01
HbA1c	1.675	0.994-2.825	0.053	0.919	0.330-2.561	0.872
Microalbuminuria	0.933	0.642-3.403	0.323			
WBC	0.955	0.809-1.129	0.592			
MPV	1.242	0.941-1.639	0.126			
Age	1.118	1.066-1.173	0.189			
Sex(male)	1.755	0.863-3.570	0.121			
CAD	0.991	0.986-1.997	0.132			
HT	0.677	0.088-5.193	0.708			
LDL	0.994	0.988-1.005	0.286			
DM during	1.027	0.982-1.074	0.238			
BMI	1.012	0.943-1.085	0.742			
Smoking	0.712	0.703-1.012	0.192			

Table 2: Univariate and Multivariate regression analyses of independent variables for AF.
NLR: Neutrophil lymphocyte ratio, MPV: Mean platelet volume, WBC: White blood cell, BMI:Body mass index, LDL: Low density lipoprotein, CRP: C reactive protein, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease.

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 NLR were also found associated with poor survival of patients with cardiovascular disease[8, 15, 16]. Many cancer survival studies have suggested that NLR 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 NLR was shown[14].

In a recent study, Gibson et al.[9] found that both preoperative and postoperative elevations in NLR 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.[19] have demonstrated that the NLR is a powerful and independent predictor of AF recurrence in patients undergoing successful cryoablation. Present study demonstrated relationship between AF and NLR and this finding was consistent with previous studies. On the contrary, Aribas et al.[20] did not reveal a association between NLR and AF recurrence after successful cardioversion. These studies which revealed association between AF and NLR confirm present study. There is a need of a new marker to indicate this relationship. In present study, NLR had a higher sensitivity and specificity. NLR 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 NLR was increased in diabetic patients with AF when compared to diabetic patients with NSR. NLR could be an important measure of systemic inflammation as it is cost effective, readily available. Increased NLR may be independent marker of atrial fibrillation in diabetic patients.

Conclusion

Our study concluded that NLR is an useful predictor of AF in diabetic patients. With this result, we thought that the NLR 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 NLR 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

1) Benjamin E LD, Vaziri S, D'Agostino R, Belanger A, P W. *Independent risk factors for atrial fibrillation in a population based cohort. The Framingham Heart Study*. JAMA : the journal of the American Medical Association 1994; 271: *840-44*.

2) Movahed MR, Hashemzadeh M, Jamal MM. *Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease*. International journal of cardiology 2005; 105: *315-18*.

3) Lin Y, Li H, Lan X et al. *Mechanism of and therapeutic strategy for atrial fibrillation associated with diabetes mellitus*. The Scientific World Journal 2013; 2013: *209428*.

4) Chung MK, Martin DO, Sprecher D et al. *C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation*. Circulation 2001; 104: *2886-91*.

5) A. Frustaci CC, F. Bellocci, E. Morgante, M.A. Russo, A. Maseri. *Histological substrate of atrial*

biopsies in patients with lone atrial fibrillation. Circulation 1997; 96: *1180-4*.

6) Imtiaz F, Shafique K, Mirza SS et al. *Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population*. International archives of medicine 2012; 5: *2*.

7) Azab B, Zaher M, Weiserbs KF et al. *Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction*. The American journal of cardiology 2010; 106: *470-6*.

8) Papa A, Emdin M, Passino C et al. *Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease*. Clinica chimica acta; international journal of clinical chemistry 2008; 395: *27-31*.

9) Gibson PH, Cuthbertson BH, Croal BL 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*.

10) *Diagnosis and classification of diabetes mellitus*. Diabetes care 2013; 36 Suppl 1: *67-74*.

11) Chobanian AV, Bakris GL, Black HR 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: the journal of the American Medical Association 2003; 289: *2560-72*.

12) Aviles RJ, Martin DO, A*pperson-Hansen C et al*. *Inflammation as a risk factor for atrial fibrillation*. Circulation 2003; 108: *3006-10*.

13) Yuan G, Zhou L, Tang J et al. *Serum CRP levels are equally elevated in newly diagnosed type 2 diabetes and impaired glucose tolerance and related to adiponectin levels and insulin sensitivity*. Diabetes research and clinical practice 2006; 72: *244-50*.

14) Chatterjee S, Chandra P, Guha G et al. *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.

15) Akpek M, Kaya MG, Lam YY 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*. The American journal of cardiology 2012; 110: *621-7*.

16) Gibson PH, Croal BL, Cuthbertson BH et al. *Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting*. American heart journal 2007; 154: *995-1002*.

17) Walsh SR, Cook EJ, Goulder F et al. *Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer*. Journal of surgical oncology 2005; 91: *181-4*.

18) Stotz M, Gerger A, Eisner F et al. I*ncreased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer*. British journal of cancer 2013.

19) Canpolat U, Aytemir K, Yorgun H et al. *Role of Preablation Neutrophil/Lymphocyte Ratio on Outcomes of Cryoballoon-Based Atrial Fibrillation Ablation*. Am. J. Cardiol. 2013.

20) Aribas A, Akilli H, Gul EE et al. *Can neutrophil/lymphocyte ratio predict recurrence of non-valvular atrial fibrillation after cardioversion?* Anadolu Kardiyol. Derg. 2013; 13: *123-30*.

21) Benjamin EJ, Levy D, Vaziri SM et al. *Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study*. JAMA: the journal of the American Medical Association 1994; 271: *840-4*.

22) Aksnes TA, Schmieder RE, Kjeldsen SE et al. *Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial)*. The American journal of cardiology 2008; 101: *634-8*.

23) Ostgren CJ, Merlo J, Rastam L, Lindblad U. *Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community*. Diabetes, obesity & metabolism 2004; 6: *367-74*.

24) Turgut O, Zorlu A, Kilicli F et al. *Atrial fibrillation is associated with increased mean platelet volume in patients with type 2 diabetes mellitus*. Platelets 2012.

25) Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. *Mean platelet volume: a link between thrombosis and inflammation?* Curr. Pharm. Des. 2011; 17: *47-58*.

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