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The role of neutrophil to lymphocyte ratio as a predictor of diastolic dysfunction in hypertensive patients

A. KARAGÖZ[1], A. VURAL[1], Z.Y. GÜNAYDIN[2], O. BEKTAŞ[2], M. GÜL[3], A. ÇELIK[4], E. UZUNOĞLU[5], S. USTA[6], A. SARITAŞ[7], Ö.U. ELALMIŞ[8]

[1]Department of Cardiology, Giresun University, Giresun, Turkey
[2]Department of Cardiology, Ordu University, Ordu, Turkey
[3]Department of Statistics, Giresun University, Giresun, Turkey
[4]Department of Cardiovascular Surgery, Giresun University, Giresun, Turkey
[5]Department of Microbiology, Giresun Prof. Dr. A. Ilhan Ozdemir State Hospital, Giresun, Turkey
[6]Department of Cardiovascular Surgery, Ahi Evren Education and Research Hospital, Trabzon, Turkey
[7]Department of Anesthesiology and Reanimation, Giresun Prof. Dr. A. Ilhan Ozdemir State Hospital, Giresun, Turkey
[8]Department of Cardiology, Numune Education and Research Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: Neutrophil to lymphocyte ratio (NLR) is a novel parameter for cardiovascular research area. The higher values of NLR have been found to be associated with worse clinical outcomes in atherosclerotic heart disease, heart failure, heart valve disease and other various cardiovascular disorders.

Although the relationship between NLR and almost all cardiovascular disorders have been investigated, the association between NLR and diastolic dysfunction remains unclear. We herein evaluated the association between NLR and diastolic dysfunction.

PATIENTS AND METHODS: The study population consisted of 41 hypertensive patients with any grade of diastolic dysfunction and 41 hypertensive patients without diastolic dysfunction determined by echocardiographic evaluation constituted the control group.

RESULTS: Mean NLR value was found to be 2.07 ± 0.82 in the diastolic dysfunction group while the control group had a mean value of 1.69 ± 0.60 (p = 0.020). The patients with diastolic dysfunction had significantly higher values of NLR. When grades of diastolic dysfunction were evaluated, NLR was 1.80 ± 0.82, 2.32 ± 0.73 and 2.75 ± 0.45 in patients with grade 1, grade 2 and grade 3 diastolic dysfunction, respectively. The patients with higher grade of diastolic dysfunction had higher values of NLR (p = 0.001). None of the other hematologic parameters differed significantly in patients with diastolic dysfunction when compared to controls.

CONCLUSIONS: Patients with diastolic dysfunction had higher values of NLR compared to subjects without diastolic dysfunction. Furthermore higher grades of diastolic dysfunction were associated with higher levels of NLR. Further studies are needed to search the possible use of NLR as a marker for prognostic stratification in diastolic dysfunction which is associated with worse cardiovascular outcomes.

Key Words:
Neutrophil to lymphocyte ratio, Diastolic dysfunction, Hypertension.

Introduction

Developments in Tissue Doppler Imaging (TDI) modalities enabled further evaluation of myocardial velocities and hence left ventricular diastolic function. Diastolic dysfunction may cause heart failure symptoms even in the patients with preserved left ventricular function[1]. Additionally, the prognostic value of diastolic dysfunction in fatal and nonfatal cardiovascular events in general population has been shown recently[2]. These findings pioneered emergence of diastolic dysfunction as a current topic in cardiovascular research area again. There is no specific therapy to improve left ventricular (LV) diastolic function directly. Thus, investigation of related parameters and if present, possible predictors, has been the focus of interest in order to prevent this process. Neutrophil to lymphocyte ratio (NLR), a novel marker, has been studied in various oncologic, hematologic, immunologic and

Corresponding Author: Ahmet Karagöz, MD; e-mail: drahmetkgz@hotmail.com

infectious diseases as well as cardiologic disorders. NLR is a simply acquirable parameter using complete blood count (CBC), which is the most commonly performed test in hospitals. This feature of easy availability leads to utilization of NLR in further research area.

NLR has been evaluated in various cardiac disorders, atherosclerotic heart disease, being in the first place. The studies revealed considerable prognostic value in addition to significant positive correlations. Predictive value of NLR in peripheral arterial disease, calcific aortic stenosis, prognostication, presence, severity and extent of coronary artery disease and many other cardiovascular disorders have already been shown[3-7]. Although the relationship between NLR and almost all cardiovascular disorders have been investigated, the importance of NLR in diastolic dysfunction remains unclear.

We herein evaluated the association between NLR and diastolic dysfunction which has already been shown to be a good predictor of fatal and nonfatal cardiovascular events in general population.

Patients and Methods

Study Protocol

The study sample was recruited from the patients examined in the outpatient clinic of Giresun University Cardiology Department. The study population consisted of 41 hypertensive patients with any grade of diastolic dysfunction and 41 hypertensive patients without diastolic dysfunction determined by echocardiographic evaluation constituted the control group. All of the hypertensive patients in both diastolic dysfunction and control groups were either newly diagnosed or were aware of hypertension without using any pharmacotherapy. Individuals already under treatment for hypertension were not included. After application of echocardiographic evaluation, the patients detected to have diastolic dysfunction were enrolled in the study group while those without diastolic dysfunction formed the control group. Blood samples of all individuals were collected on the day of admission and NLR was calculated via division of neutrophil count by the number of lymphocytes. Exclusion criteria were presence of malignancy, active infection, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, atrial fibrillation, connective tissue or other chronic inflammatory diseases, rheumatic valvular disease and prosthetic heart valves. Informed consent was obtained from all of the participants and the study was approved by the local ethical committee.

Echocardiographic Assessment

Echocardiographic assessment was performed with Hitachi Aloka prosound a6 echocardiography device by using 2.5-3.5 MHz transducer in the lateral decubitis position according to American Echocardiography Association guidelines with simultaneously recorded electrocardiogram. The evaluation was performed by an experienced physician aware of study design. Left atrium diameter was measured on M-mode tracing at aortic sinus Valsalva level in the parasternal long axis view. Left ventricle end-systolic diameter, left ventricle end-diastolic diameter, posterior wall and interventricular septum thickness were measured on the M-mode tracing at the papillary muscle level. As a practical approach to the diagnosis of diastolic dysfunction, the American Society of Echocardiography proposes measurement of the mitral annulus early diastolic velocity (Ea) via tissue Doppler imaging (TDI) in the first instance[8]. Diastolic dysfunction is diagnosed if lateral Ea is measured to be below 10 cm/sec. Then for the grading of diastolic dysfunction, the ratio of transmitral early (E) and late (A) velosities (E/A) and E/Ea ratio measured by pulse Doppler is guiding. The values of $E/A < 0.8$ and $E/Ea \leq 8$ leads to the diagnosis of mild diastolic dysfunction (impaired relaxation pattern) while E/A between 0.8-1.5 and E/Ea between 9-12 signifies moderate diastolic dysfunction (pseudonormal phase). Finally, $E/A \geq 2$ and $E/Ea \geq 13$ indicates severe diastolic dysfunction. To this end, transmitral flow samples were obtained by placing the sample volume of PW Doppler to the edges of mitral leaflets in the apical four-chamber view. Mitral E, A waves, E/A ratio and DT of the E wave were calculated from these tracings. Then, again in the apical four-chamber view, after appropriate gain settings were adjusted, lateral and septal diastolic velocities (lateral Ea and septal Ea) were measured by tissue Doppler imaging.

Statistical Analysis

Analyses were performed, using the MedCalc® (Version 11.3.8.0) pocket program. The data were expressed as the mean ± standard deviation (SD) and were tested for normal distribution using the Kolmogorov-Smirnov test.

Comparisons between patients were made by using Student's independent *t*-test for normally distributed data and the Mann-Whitney U test for non-normal distributed data. When comparing patients in terms of grade of diastolic dysfunction One-Way ANOVA test was used for normally distributed data and Kruskal-Wallis H test for non-normal distributed data. Pearson's correlation coefficient was used to measure of the strength of the association between the two variables. The results were regarded as significant when $p < 0.05$.

Results

A total of 82 hypertensive patients were enrolled in the study. The mean age was 50.05 ± 6.30 in the study group consisting of 41 hypertensive patients with diastolic dysfunction while it was 48.49 ± 7.44 in the control group ($p = 0.670$). The control group comprised of 41 hypertensive patients without diastolic dysfunction. The study group consisted of 27 female and 14 male patients while there were 25 female and 16 male patients in the control group ($p = 0.819$). Baseline characteristics of diastolic dysfunction and control groups were compared and the results are given in Table I. Systolic blood pressure, heart rate, serum high density lipoprotein (HDL), and triglyceride levels differed significantly between two groups ($p < 0.05$). There was no statistically significant difference between two groups by the means of body mass index, body surface area, diastolic blood pressure, serum low density lipoprotein, fibrinogen and C-reactive protein (CRP) levels and erythrocyte sedimentation rates ($p > 0.05$). When echocardiographic parameters were evaluated, we did not notice any significant difference in terms of left ventricular end-systolic (LVESD) and end-diastolic diameters (LVEDD) ($p > 0.05$). On the other hand, while the groups were formed considering whether diastolic dysfunction was present or not, interventricular septum and posterior wall thickness, left ventricular mass index (LVMI) and left atrium volume index (LAVI) were found to be

Table I. Comparison of baseline characteristics, echocardiographic and laboratory findings and neutrophil to lymphocyte ratio.

	Diastolic dysfunction group	Control group	*p*
Age	50.05 ± 6.30	48.49 ± 7.44	0.670
Gender (M/F)	14/27	16/25	0.819
BMI	31.90 ± 5.13	29.79 ± 3.46	0.097
BSA	1.87 ± 0.14	1.85 ± 0.20	0.601
SBP	160.83 ± 11.69	151.61 ± 6.38	0.001
DBP	95.66 ± 6.56	94.59 ± 4.86	0.608
HR	77.17 ± 11.59	70.61 ± 8.80	0.005
LDL-C	119.32 ± 30.87	112.94 ± 34.05	0.247
HDL-C	47.07 ± 11.46	52.88 ± 12.57	0.035
TRG	161.73 ± 69.42	126.49 ± 61.40	0.017
Sedimentation	12.56 ± 4.88	11.61 ± 4.75	0.109
Fibrinogen	304.07 ± 46.18	287.20 ± 45.90	0.101
CRP	0.24 ± 0.14	0.23 ± 0.18	0.754
LVEF	65.07 ± 3.70	65.59 ± 2.90	0.644
LVEDD	4.38 ± 4.38	4.52 ± 0.43	0.223
LVESD	2.68 ± 0.49	2.71 ± 0.31	0.685
IVS	1.16 ± 0.19	0.88 ± 0.13	0.001
PW	1.17 ± 0.14	0.98 ± 0.13	0.001
Septal Ea	6.32 ± 0.99	9.88 ±1.18	0.001
Lateral Ea	8.02 ± 1.04	14.75 ± 1.90	0.001
LVMI	97.84 ± 21.43	76.04 ± 15.65	0.001
LAVI	23.82 ± 4.21	18.71 ± 3.97	0.001
NLR	2.07 ± 0.82	1.69 ± 0.60	0.020

BMI: Body mass index, BSA: Body surface area, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TRG: Triglyceride, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle end-systolic diameter, IVS: Interventricular septum, PW: Posterior wall, LWMI: Left ventricular mass index, LAVI: Left atrial volum index, N/L: Neutrophil to lymphocyte ratio.

significantly higher and septal and lateral Ea were significantly lower in patients with diastolic dysfunction ($p < 0.001$). Patients with diastolic dysfunction had significantly higher values of NLR when compared to control group. Mean NLR value was found to be 2.07±0.82 in the study group while the control group had a mean value of 1.69±0.60 ($p = 0.020$). Other parameters of complete blood count (CBC) were also evaluated. Red cell distribution width (RDW-SD), mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet crit (PCT), platelet distribution width (PDW) did not differ significantly between two groups ($p > 0.05$). The mean value of platelet to lymphocyte ratio (PLR), another novel parameter in cardiovascular research area, was also similar between groups ($p = 0.854$) (Table II).

In the second phase of the study, patients with diastolic dysfunction were divided into three groups according to grade of diastolic dysfunction. The number of patients with grade 1 diastolic dysfunction was 24. Grade 2 diastolic dysfunction was present in 12 patients and there were 5 patients with grade 3 diastolic dysfunction. Comparison of grades of diastolic dysfunction in terms of NLR and other parameters is shown in Table III. Patients with grade 3 diastolic dysfunction had the highest values of NLR while patients with grade 1 had the lowest ($p = 0.001$). E/A, E/Ea, deceleration time (DT) and LVMI differed significantly between three groups ($p < 0.05$). However, difference between LAVI, which is also known to be a beneficent predictor of diastolic dysfunction, did not reach a statistical significance ($p = 0.173$). In addition, NLR had positive correlation with E/A and E/Ea and negative correlation with DT. We could not establish a meaningful correlation between NLR and cardiac mass and dimension indexes, such as LVMI and LAVI.

Discussion

Diastolic dysfunction is usually disregarded when compared with systolic disorders. On the other hand, it may cause challenges in clinical practice and also has prognostic significance. In fact, presence of diastolic dysfunction is a silent sign of development of both heart failure symptoms and adverse cardiac events[9]. In epidemiological studies, the percentage of patients with heart failure with preserved ejection fraction (HFpEF) ranges from 40% to 71% (mean 56%), but in hospital-based cohort studies it is slightly lower, ranging from 24% to 55% (mean 41%)[10]. Despite better LVEF, HFpEF has a prognosis similar to that observed in HF patients with reduced LVEF, with a mortality rate exceeding 20% in 1 year[11]. NLR has emerged as a new marker for various diseases including cardiovascular disorders. The prognostic value of NLR has been demonstrated in cancer patients[12-17]. Besides carrying a predictive significance in many malignant diseases, it was also found to be associated with pulmonary disorders such as cystic fibrosis, chronic obstructive pulmonary disease and acute pulmonary embolism[18-20]. Diabetic nephropathy, retinopathy and gestational diabetes mellitus in pregnant women can also be noted as conditions that NLR was evaluated and significant positive correlations were found[21-23]. The predictive value of NLR in stroke subtypes and transient ischemic attack has been demonstrated[24]. In addition, as

Table II. Evaluation of other hematological parameters.

	Diastolic dysfunction group	Control group	p
RDW-SD	42.8 ± 4.22	41.27 ± 3.36	0.073
MPV	10.03 ± 1.20	10.14 ± 1.24	0.684
MCV	88.0780 ± 6.68807	87.71 ± 8.18	0.636
MCH	28.14 ± 2.52	28.53 ± 1.69	0.416
PCT	0.26 ± 0.07	0.26 ± 0.06	0.966
PDW	16.01 ± 0.43	16.13 ± 0.54	0.283
NLR	2.07 ± 0.82	1.69 ± 0.60	0.020
PLT/L	118.16 ± 36.21	121.34 ± 38.28	0.854

RDW-SD: Red cell distribution width, MPV: Mean platelet volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PCT: Platelet crit, PDW: Platelet distribution width, N/L: Neutrophil to lymphocyte ratio, PLT/L: Platelet to lymphocyte ratio.

Table III. Evaluation of neutrophil to lymphocyte ratio between grades of diastolic dysfunction.

	Grade 1	Grade 2	Grade 3	*p*
NLR	1.80 ± 0.82	2.32 ± 0.73	2.75 ± 0.45	0.001
E/A	0.67 ± 0.12	1.03 ± 0.16	2.12 ± 0.09	0.001
E/Ea	6.90 ± 0.97	11.43 ± 1.39	14.82 ± 3.41	0.001
DT	219.50 ± 13.42	183.75 ± 7.29	146.60 ± 12.74	0.001
LVMI	90.86 ± 23.14	109.34 ± 16.06	103.75 ± 8.62	0.037
LAVI	22.78 ± 4.48	25.15 ± 3.75	25.59 ± 2.77	0.173

N/L: Neutrophil to lymphocyte ratio, DT: Deceleration time, LVMI: Left ventricular mass index, LAVI: Left atrial volume index.

mentioned above, this has also been the subject of various studies in the cardiovascular research area. Most popular issue has certainly been coronary artery disease. NLR was found to have predictive value in detection of presence, severity and extent of coronary artery disease[4,5]. It has been used in prediction of coronary artery disease mortality, prognostication of ST-elevation myocardial infarction (STEMI), assessment of stent thrombosis risk and development of coronary collateral circulation in patients with chronic total occlusion[7,25-27]. A strong association was also found between NLR and TIMI flow grade in patients with STEMI undergoing primary percutaneous coronary intervention[28]. The basic mechanism for impairment of NLR was thought to be a mild ongoing proinflammatory process in almost all of these disorders. The presence of such an inflammatory process in diastolic dysfunction and HFpEF has also been demonstrated by the increase of various inflammatory markers previously[29]. Therefore, the impairment of NLR may also be present in diastolic dysfunction and may be attributed to this proinflammatory process in the absence of an infection. Beyond atherosclerotic disorders, NLR was also found to be associated with idiopathic dilated cardiomyopathy, mitral annular calcification, coronary artery ectasia, infective endocarditis, arterial stiffness, coronary calcium score, atrial septal aneurysm and even spontaneous echocardiographic contrast in patients with rheumatic mitral stenosis[30-36]. Yildiz et al[37] demonstrated the association between the NLR and the presence of ventricular premature contractions in young adults. However, NLR was not found to be a predictor for new onset atrial fibrillation following coronary bypass surgery[38]. Furthermore, it was proposed that NLR may predict left atrial thrombus in patients with nonvalvular atrial fibrillation[39]. Sunbul et al[40] stated that patients with non-dipper hypertension had significantly higher NLR and platelet to lymphocyte ratio (PLR) values compared to dipper hypertension. As diastolic dysfunction frequently leads to heart failure symptoms, it will be appropriate to put an emphasis on the association between NLR and heart failure. The study of Tasal et al[41] revealed that higher NLR after levosimendan infusion is associated with an increased risk of in-hospital mortality in patients with acute decompensated heart failure. In almost all of these studies, higher NLR was associated with worse clinical outcomes. While strong associations were detected with many disorders in cardiovascular research area, there is still no study evaluating the relationship between NLR and diastolic dysfunction, which is much more important than estimated in terms of cardiovascular morbidity and mortality. We designed this study to investigate a possible association between NLR and diastolic dysfunction. Patients with diastolic dysfunction had significantly higher values of NLR. When grades of diastolic dysfunction were evaluated, the patients with grade 3 diastolic dysfunction had the highest values of NLR while patients with grade 1 had the lowest, supporting an association between diastolic dysfunction and NLR. Moreover, there was a positive correlation between NLR and determinants of diastolic dysfunction such as E/A and E/Ea. Generally, patients with higher grades of diastolic dysfunction have shorter deceleration time (DT). Compatible with this information, we also determined a negative correlation between NLR ratio and DT. NLR can be potentially affected by conditions such as metabolic syndrome, valvular heart disease, abnormal thyroid function tests, renal or hepatic dysfunction, local or systemic infection and ingestion of anti-inflammatory drugs[42]. Therefore, patients with the above-mentioned features were not included in the study. We enrolled patients with new-onset hypertension without use

of any antihypertensive drugs in both diastolic dysfunction and control groups to eliminate the effects of hypertension as a possible confounder. Hence the difference in NLR levels can conveniently be attributed to presence of diastolic dysfunction. On the other hand another novel biomarker, platelet to lymphocyte ratio did not differ between two groups as well as other hematological parameters such as RDW, MPV, MCV, MCH, PCT and PDW.

The strength of the association was enhanced via evaluation of almost all diastolic dysfunction parameters including LVMI and LAVI. All possible confounders that are likely to affect NLR were excluded. In the light of these findings, it can be suggested that the significant difference in the NLR results from presence of diastolic dysfunction. On the other hand, there is no universally accepted cut-off value for NLR which predicts a negative outcome. Normal NLR value is stated to vary between < 1.4 and < 6 in the afore mentioned studies. Herein we did not need to settle a cut-off value as we did not perform a prognostic stratification using tertiles.

Conclusions

Patients with diastolic dysfunction had higher values of NLR when compared to subjects without diastolic dysfunction. Furthermore, higher grades of diastolic dysfunction were associated with higher levels of NLR. There was a positive correlation between NLR and determinants of diastolic dysfunction such as E/A and E/Ea. DT correlated negatively with NLR. Further studies are needed to search the possible use of NLR as a marker for prognostic stratification in diastolic dysfunction, which is associated with worser cardiovascular outcomes than estimated without an exactly clarified mechanism.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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