Does Neutrophil to Lymphocyte Ratio Tell Something About Atherosclerosis in Hemodialysis Patients?

Hemodiyaliz Hastalarında Nötrofil Lenfosit Oranı Aterosklerozu mu Gösteriyor?

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ABSTRACT

OBJECTIVE: Atherosclerotic cardiovascular disease (CVD) is an important cause of mortality and morbidity in end-stage renal disease (ESRD). Atherosclerotic changes in carotid arteries show the extent of systemic atherosclerosis. Carotid intima media thickness (CIMT) can be measured by ultrasonography. Inflammation is included in pathogenesis of atherosclerosis. Neutrophil to lymphocyte ratio (NLR) may show inflammation and the patients who has higher cardiovascular risk. The aim of this study was to detect the relationship between NLR, C-reactive protein and CIMT.

MATERIAL and METHODS: 75 hemodialysis patients (42 female, 33 male) were included in this study. Patients with active infection, known malignancy and a cardiovascular disease were excluded. CIMT was measured by B mode ultrasonography. Patients' laboratory parameters at the time of inclusion were noted and NLR was calculated.

RESULTS: Mean age was 58.07±16.23 years and 44% of the patients were male. Mean dialysis vintage was 79.27±67.06 months. In correlation analysis, CIMT was positively correlated with age, CRP and NLR (respectively r=.380 p=.001; r=.255 p=.005; r=.283 p=.014). By regression analysis age (β=.527, p=0.00), CRP (β=.419, p=0.001) and NLR (β=.251, p=0.022) were found to be independent determinants of CIMT.

CONCLUSION: NLR was found to be independently correlated with CIMT in haemodialysis patients and may be used in cardiovascular risk assessment in clinical practice.

KEY WORDS: Neutrophil to lymphocyte ratio, Haemodialysis, Cardiovascular disease

ÖZ

AMAÇ: Son dönem böbrek yetmezliğinde (SDBY) kardiyovasküler hastalık mortalite ve morbiditenin en önemli nedenidir. Aterosklerozun göstergesi olan karotis intima medya kalınlığında (KİMK) artış SDBY de kardiyovasküler hastalığın bir belirtecidir. İnflamasyon aterosklerozun patogenezinde rol oynamaktadır. Beyaz küre sayısının kardiyovasküler olaylar için bağımsız bir belirteç olduğu bildirilmektedir. Nötofil- lenfosit oranı (NLO) kardiyovasküler olaylar açısından risk altında olan hastaları gösterebilir. SDBY nedeniyle hemodiyalize giren hastalarda ateroskleroz belirteci olan KİMK ile NLO ve CRP arasında ilişki olup olmadığını araştırmayı hedefledik.

GEREÇ ve YÖNTEMLER: Bu kesitsel çalışmaya hastanemiz hemodiyaliz ünitesinde en az 6 aydır hemodiyalize giren, bilinen aktif enfeksiyonu, kardiyovasküler hastalığı, malignitesi olmayan 75 hasta (42 kadın, 33 erkek) dahil edildi. Hastaların KİMK'ları B mod ultrasonografi kullanılarak ölçüldü. Hastaların çalışmaya dahil edildikleri andaki laboratuvar parametreleri kaydedilerek nötrofil lenfosit oranları hesaplandı.

BULGULAR: Ortalama yaş 58.07±16.23 yıl idi ve hastaların %44 ü erkek idi. Ortalama diyaliz süresi 79,27±67,06 ay idi. Yapılan korelasyon analizinde KİMK nın yaş, CRP ve NLO ile pozitif korele olduğu tespit edildi (sırasıyla r=,380 p=,001 ; r=,255 p=,005; r=,283 p=,014). Yapılan regresyon analizinde yaş (β=,527, p=0,00), CRP (β=,419, p=0,001) ve NLO (β=,251, p=0,022) nun KİMK nın bağımsız belirleyicileri olduğu tespit edildi.

SONUÇ: SDBY nedeniyle hemodiyalize giren hastalarda yüksek NLO bağımsız olarak KİMK ile ilişkilidir ve klinik pratikte kardiyovasküler risk değerlendirilmesinde kullanılabilir.

ANAHTAR SÖZCÜKLER: Nötrofil lenfosit oranı, Hemodiyaliz, Kardiyovasküler hastalık

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INTRODUCTION

Cardiovascular (CV) disease is the most common cause of mortality in end-stage renal disease (ESRD) patients, accounting for nearly 40% of all-cause mortality (1). Many risk factors and immune changes in the uremic milieu may be related to increased risk of CVD in this population (2) Multiple traditional and non-traditional cardiovascular risk factors take part in the atherosclerotic process Traditional risk factors including diabetes mellitus, hypertension, dyslipidaemia, and obesity cannot completely explain the increased risk (3). As novel risk factors for CVD, inflammation and protein-energy wasting (PEW) are highly prevalent in ESRD patients, and may play a more important role in CVD in these patients than traditional risk factors (4).

As a sign of atherosclerosis, increased carotid intima-media thickness (CIMT) has been widely used and is accepted as a strong predictor of cardiovascular events and mortality in ESRD patients (5).

The neutrophil count increases in inflammation and the lymphocyte count is related to malnutrition and general stress. NLR may be sensitive in detecting cardiovascular risk. NLR was found to be associated with increased adverse outcomes in oncologic (6) and cardiovascular diseases(7-9). In chronic kidney disease (CKD), NLR was related to renal functional deterioration (10) and endothelial dysfunction (11). Besides, NLR was associated with cardiovascular events and shown to be a predictor of future events (12).

In this study, we aimed to evaluate the association between NLR and IMT as an indicator of atherosclerosis in hemodialysis patients.

PATIENTS and METHODS

The study protocol was approved by the Medical Ethics Comittee of Diskapi Yildirim Beyazit Training and Research Hospital. Written informed consent was obtained from all subjects included in the study.

This was a cross-sectional study involving 75 ESRD patients (33 males, 42 females; mean age, 58.07±17.25 years) receiving HD for ≥6 months at the dialysis unit of Diskapi Yildirim Beyazit Training and Research Hospital between March and May 2012.

Patients aged 21-80 years willing to participate were screened. A review of the medical records (including age, sex, and duration of renal replacement therapy, medications and primary disease causing ESRD) was performed. Exclusion criteria were as follows: 1. nephrotic range proteinuria, 2. active infection, 3. known malignancy, 4. autoimmune disease, 5. known cardiovascular disease.

A total of 75 patients fulfilled the criteria and were enrolled in the study. They were all on 3 times per week dialysis for 4 hours with standard bicarbonate containing dialysate using a biocompatible HD membrane (Polysulfone, FX-80 series, Fresenius, Germany). Dialysate flow rates were 500 mL/min and blood flow rates were 250-300 mL/min. A total of 32 patients (42.7%) used antihypertensive treatment.

Biochemical Analyses

Venous blood samples for biochemical analyses were drawn before the midweek session. Serum total cholesterol and triglyceride levels were measured by colorimetric analysis (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, cMannheim, Germany). High-density lipoprotein cholesterol was measured by the phosphotungstic acid precipitation method. C-reactive protein was measured by the immunonephelometric method (IMECE). Other biochemical parameters were measured using a computerised auto analyser (Hitachi 717; Boehringer-Mannheim).

Definition of NLR

Complete blood count with automated differential counts was obtained. NLR was calculated as the ratio of neutrophils and lymphocytes.

CIMT Measurements

Ultrasonographical B-mode imaging of bilateral carotid arteries was performed with high-resolution real-time ultrasonograph with a 12MHz linear-assay transducer (Mindray DC7, China). Evaluations were performed by a single trained radiologist who was blinded to the clinical status and laboratory parameters of the patients. Carotid arteries, carotid bulb and internal carotid arteries were examined by two different longitudinal projections. At each longitudinal projection, CIMT was conducted from the site of the greater thickness. CIMT was defined as the distance between the leading edges of the lumen interface at the far wall in plaque-free arterial segments. The value was expressed as an average of the maximal CIMT

Statistical Analysis

Statistical analysis was performed by using the statistical package SPSS version 19.0 (SPSS Inc., IL, USA). All variables were expressed as the mean±SD unless otherwise indicated. Dichotomous variables were compared using the chi-square test. Statistical differences between parametric data of two groups were analysed using the Student's t-test. The Mann-Whitney U test was used to determine differences between nonparametric data. Linear associations between continuous variables were assessed using the Spearman correlation test. Parameters found to be correlated are analyzed by linear regression analyzis.

RESULTS

Baseline characteristics of 75 HD patients are shown in Table I and treatment characteristics in Table II. The etiology of ESRD patients was diabetic nephropathy (n=19), chronic glomerulonephritis (n=15), hypertensive nephropathy (n=20), chronic pyelonephritis (n=2), polycystic kidney disease (n=3), and unknown (n=16).

Table I: Laboratory results of the patients.

Parameters	Patients (n=75)
Age	58.07±17.25
Male/female	33/42
BMI (kg/m²)	25.8±5.1
Dialysis vintage (months)	79.3±69.1
SBP (mm Hg)	124.9±16.3
DBP (mm Hg)	77.3±10.3
Hemoglobin (mg/dL)	10.59±1.34
Albumin (gr/dL)	3.6±0.5
Total cholesterol (mg/dl)	157.9±43.2
Triglyceride (mg/dl)	150.8±84.2
Uric acid (mg/dl)	5.8±1.4
CRP (mg/L)	2.21±1.9
CIMT (mm)	0.87±2.1
NLR	4.38±2.72

BMI: Body mass index, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **CRP:** C-reactive protein, **NLR:** Neutrophil-to-lymphocyte ratio

We found that 19 of the patients had DM and 32 had HT. None of the patients had residual renal function. Mean IMT of the patients was 0.87±0.2 mm.

The patients were distributed into two groups according to the median value of NLR (group A NLR ≤3.5 and group B NLR >3.5). There was no statistically significant difference in terms of age (p=0.125), dialysis vintage (p=0.07), body mass index (BMI) (p=0.8), hemoglobin (p=0.164) and uric acid levels (p=0.327). The albumin level was statistically significantly lower in Group B (3.8±0.4 gr/dl vs 3.2±0.4 gr/dl; p=0.049). Also triglyceride and cholesterol were found to be lower in Group B (175.2±39.4 mg/dl vs 143.1±40.8 mg/dl; p=0.001 and 179.5±99 mg/dl vs 125.5±57.6 mg/dl; p=0.006 respectively). C-reactive protein (CRP) level and CIMT were higher in group B (1.2±1.6 mg/L vs 2.7±3.0 mg/L; p=0.007 and 0.84±0.2 mm vs 0.87±0.18 mm; p=0.04 respectively) (Table III).

NLR was found to be positively correlated with CIMT (r=0.283, p=0.014), CRP (r=0.290, p=0.011) and negatively correlated with albumin (r=-0.252, p=0.03), total cholesterol (r=-0.341, p=0.003) and triglyceride (r=-0.265, p=0.024) levels.

Correlation analysis of CIMT was performed and it was found to be positively correlated with age, CRP and NLR (respectively r=0.380 p=0.001; r=0.255 p=0.005; r=0.283 p=0.014). Correlation of CIMT with NLR can be seen in Figure 1.

Table II: Treatment characteristics.

Treatment characteristics	%(n)
Beta-blocker	30.7 (23)
Alpha-blocker	2.7 (2)
RAS inhibitors	24 (18)
Ca channel blocker	26.2 (20)
Iron	69.3 (52)
ESA	86.7 (65)
HMGCoa-reductase inhibitors	2.7 (2)

RAS: Renin-angiotensin inhibitors, **ESA:** Erythropoiesis stimulating agent

Table III: Parameters compared in terms of the NLR group.

	Group A (NLR≤3.5)	Group B (NLR>3.5)	p
Age (years)	54.3±14.1	58.9±17.1	0.125
Dialysis vintage (months)	126.6±17.1	123.5±15.6	0.07
BMI (kg/m²)	24.1±4.0	27.3±10.53	0.8
Hemoglobin (mg/dl)	10.9±1.2	10.5±1.5	0.164
Albumin (gr/dl)	3.8±0.4	3.2±0.4	**0.049**
Total cholesterol (mg/dl)	175.2±39.4	143.1±40.8	**0.001**
Triglyceride (mg/dl)	179.5±99	125.4±57.6	**0.006**
Uric acid (mg/dl)	5.5±1.0	6.0±1.7	0.327
CRP (mg/L)	1.2±1.6	2.7±3.0	**0.007**
CIMT (mm)	0.84±0.2	0.87±0.18	**0.04**

BMI: Body mass index, **CRP:** C-reactive protein, **NLR:** Neutrophil-to lymphocyte ratio

Table IV: Regression analysis for CIMT.

		B	Std. error	Beta	t	Significance
1	(Constant)	.283	.107		2.635	.011
	Age	.007	.001	.527	4.632	.000
	CRP	.048	.013	.419	3.658	.001
	NLR	.019	.008	.251	2.356	.022

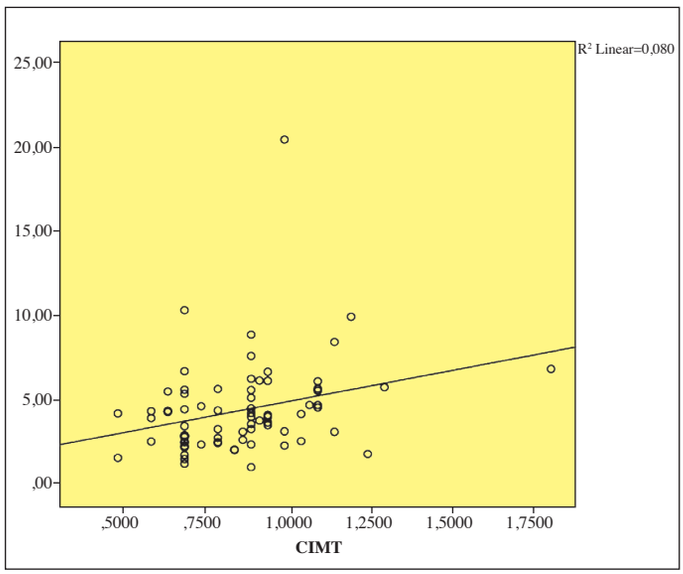

Figure 1: *Correlation of CIMT with NLR.*

The parameters found to be correlated with CIMT were analysed by linear regression analysis and age (β=, 527, p=0, 00), CRP (β=, 419, p=0,001) and NLR (β=.251, p=0,022) were found to be independent determinants of CIMT; R^2 was 0.447 (Table IV)

DISCUSSION

There are two findings of this cross-sectional study. First, NLR is positively correlated with CRP and negatively correlated with cholesterol, triglyceride and albumin levels in HD patients.

Secondly, CIMT is positively correlated with NLR, age and CRP and this relation persists after regression analysis.

The malnutrition-inflammation-atherosclerosis (MIA) syndrome is a well defined syndrome in ESRD patients (13). CRP and other cytokines are increased in HD patients (14-16). Inflammation has a central role in the pathogenesis of atherosclerosis (13). NLR is being used as a new inflammatory marker in many diseases to identify higher risk patients (7-9,16,17). In a study, NLR was found to be associated with the severity of coronary artery disease and 30year survival (7). In patients with peripheral arterial disease NLR was associated with ischemic event risk (9). In a cross-sectional study in 2013, NLR was positively correlated with IL-6 and CRP while negatively correlated with serum albumin levels in predialysis and dialysis patients. In a study in patients with CKD stage 4, high LR was shown to be associated with worse prognosis and to rapidly progress to RRT (10). In a study of Solak et al., higher NLR was associated with endothelial dysfunction and cardiovascular events (11).

Tomoko et al. also reported NLR to be related to increased cardiovascular events as well as being a stronger predictor of future events in ESRD (12).

In our study CIMT was found to be positively correlated with CRP, NLR and age and this relation persisted after regression analysis. Moreover, patients with higher NLR had higher CRP and CIMT levels.

In this study we also found a negative correlation between NLR and serum albumin, total cholesterol, triglyceride levels. These results are compatible with protein energy wasting syndrome in ESRD patients and may be associated with reverse epidemiology in this population (18).

Calculation of NLR is very simple and cheap when compared with the other inflammatory cytokines (19). As a sign of atherosclerosis, increased CIMT has been widely used and accepted as a strong predictor of cardiovascular events and mortality in ESRD patients (20). Therefore this simple, relatively inexpensive and universally available method can be used not only for detection of inflammation but also the prediction of high-risk patients together with CIMT.

The limitations of our study were the relatively small sample size and cross-sectional nature of the study.

In conclusion, NLR was correlated with CIMT in hemodialysis patients and can be useful in cardiovascular risk assessment. Further well-designed, randomized, and controlled trials evaluating the relationship between NLR and CVD in ESRD patients are needed.

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