# Neutrophil-to-lymphocyte ratio as a possible indicator of epicardial adipose tissue in patients undergoing hemodialysis

Adalet Ozcicek[1], Fatih Ozcicek[1], Gursel Yildiz[2], Aysu Timuroglu[1], Levent Demirtas[1], Mutlu Buyuklu[3], Ufuk Kuyrukluyildiz[4], Emin Murat Akbas[5], Ergun Topal[3], Kultigin Turkmen[6]

[1]Department of Internal Medicine, School of Medicine, Erzincan University, Erzincan, Turkey
[2]Department of Nephrology, Atatürk State Hospital, Zonguldak, Turkey
[3]Department Cardiology, School of Medicine, Erzincan University, Erzincan, Turkey
[4]Department of Anesthesiology and Reanimation, School of Medicine, Erzincan University, Erzincan, Turkey
[5]Department of Internal Medicine, Division of Endocrinology and Metabolism, School of Medicine, Erzincan University, Erzincan, Turkey
[6]Department of Internal Medicine, Division of Nephrology, School of Medicine, Erzincan University, Erzincan, Turkey

**Corresponding author:**
Adalet Ozcicek
Department of Internal Medicine
School of Medicine
Erzincan University
24100 Erzincan, Turkey
Phone: +90 5052104083
Fax: +90 4462122211
E-mail: draozcicek@hotmail.com

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## Abstract

**Introduction:** Chronic inflammation is a major risk factor in the pathogenesis of cardiovascular disease in end-stage renal disease (ESRD) patients. Epicardial adipose tissue (EAT) is the true visceral fat depot of the heart. The relationship between coronary artery disease and EAT was shown in healthy subjects and ESRD patients. In the present study we aimed to investigate the relationship between EAT and inflammation parameters including neutrophil-to-lymphocyte ratio (NLR) in hemodialysis (HD) patients.
**Material and methods:** Forty-three HD patients (25 females, 18 males; mean age: 64.1 ±11.9 years) receiving HD and 30 healthy subjects (15 females, 15 males; mean age: 59.1 ±10.8 years) were enrolled in the study. Epicardial adipose tissue measurements were performed by echocardiography.
**Results:** Neutrophil-to-lymphocyte ratio levels were significantly higher in HD patients than in the healthy control group. Hemodialysis patients were separated into two groups according to their median value of NLR (group 1, NLR < 3.07 ($n$ = 21) and group 2, NLR ≥ 3.07 ($n$ = 22)). Group 2 patients had significantly higher EAT, C-reactive protein and ferritin levels, while albumin levels were significantly lower in this group. In the bivariate correlation analysis, EAT was positively correlated with NLR ($r$ = 0.600, $p$ < 0.001) and ferritin ($r$ = 0.485, $p$ = 0.001) levels.
**Conclusions:** Neutrophil-to-lymphocyte ratio was found to be an independent predictor of EAT in HD patients (odds ratio = 3.178; $p$ = 0.008). We concluded that this relationship might be attributed to increased inflammation in uremic patients.

**Key words:** epicardial adipose tissue, neutrophil-to-lymphocyte ratio, inflammation, end-stage renal disease.

## Introduction

Despite the improvements in diagnostic tools and medical applications, cardiovascular diseases (CVD) remain the most common cause

of morbidity and mortality in patients with end-stage renal disease (ESRD) receiving hemodialysis (HD) [1, 2]. Beside traditional risk factors including hypertension, diabetes mellitus, dyslipidemia, advanced age and left ventricular hypertrophy (LVH), novel risk factors such as endothelial dysfunction (ED), vascular calcification (VC), oxidative stress, and inflammation are highly prevalent and seem to play a more important role for vascular disease in renal patients compared to healthy subjects [3–7]. Among the risk factors mentioned above, atherosclerosis, inflammation and VC were found to be the most commonly encountered factors in the pathogenesis of CVD in ESRD patients [8, 9].

Epicardial adipose tissue (EAT) originates from the splanchnopleuric mesoderm [10] and is also accepted as the true visceral fat depot of the heart that accounts for approximately 20% of total heart weight and covers 80% of the cardiac surfaces, mostly in the grooved segments along the paths of coronary arteries [11–13]. Recent studies have shown a close relationship between coronary artery disease (CAD) and EAT by using multidetector computed tomography (MDCT) and echocardiography in healthy subjects and in patients with high risk of CAD [14–17].

Mazurek *et al.* [15] concluded that, like abdominal visceral adipose tissue, EAT is also metabolically active because it can secrete proinflammatory cytokines and utilize free fatty acids (FFAs). In recent studies, the authors concluded that EAT acts as an extremely active organ that produces several bioactive adipokines, as well as proinflammatory and proatherogenic cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-6, resistin, visfatin, omentin, leptin, plasminogen activator inhibitor-1 (PAI-1) and angiotensinogen [15, 18–21]. In addition, abdominal subcutaneous fat tissue was also found to be closely associated with inflammation in physiologic conditions such as pregnancy [22].

Turkmen *et al*. [23] recently demonstrated that EAT is increased in HD and PD patients and this active visceral fat tissue is closely related to malnutrition-inflammation-atherosclerosis/calcification (MIAC) syndrome in this population. Thereafter, the authors also observed the close relation between visceral fat tissue including both epicardial and periaortic fat thickness, inflammation and coronary artery calcification in PD and hemodialysis patients [24].

The ESRD patients also have increased serum levels of inflammatory mediators including high-sensitivity C-reactive protein (hs-CRP), TNF-α and IL-6 [25]. In recent years, neutrophilia and relative lymphocytopenia were shown to be an independent predictor of mortality in patients with acute heart failure [26, 27]. Moreover, neutrophil-to-lymphocyte ratio (NLR) was introduced as a potential marker to determine inflammation in renal and cardiac disorders [28–32].

Neutrophil-to-lymphocyte ratio was also shown as a predictor of long-term mortality in patients who underwent percutaneous coronary intervention [33]. These studies collectively demonstrated the importance of white blood cells including neutrophils and lymphocytes in the pathogenesis of atherosclerosis in the general population.

The exact relationship between vascular calcification and inflammatory parameters including NLR was also demonstrated by the studies done by our group in HD patients [34].

To date in the literature, there has been no study investigating the association between novel inflammatory markers and EAT in HD patients.

In the present study, we aimed to investigate the relationship between EAT, CRP and NLR in ESRD patients receiving HD and to compare these results with others obtained from healthy subjects.

## Material and methods

The study protocol was approved by the Medical Ethics Committee of Erzincan University (School of Medicine, Erzincan, Turkey) in 2012. This was a cross-sectional study involving 43 HD patients receiving HD for ≥ 6 months in the Hemodialysis Unit of Erzincan University Mengücek Gazi Training and Research Hospital and 30 healthy control subjects. Exclusion criteria were: (i) congestive heart failure; (ii) the presence of active infections; (iii) autoimmune disease. Hemodialysis modality includes conventional 4-h HD three times a week with polysulfone dialyzers. A 250 ml/min (range: 200–300 ml/min) of mean blood flow rate was obtained during dialysis sessions. Demographic data, medications and dialysis duration of ESRD were recorded.

### Biochemical analyses

Venous blood samples for biochemical analyses were drawn after at least 10 h of fasting before taking any medication at a single midweek dialysis session. All biochemical analyses were undertaken using an oxidase-based technique at Roche/Hitachi Modular System (Mannheim, Germany) in the Central Biochemistry Laboratory of the Erzincan University School of Medicine, Mengücek Gazi Training and Research Hospital.

### Echocardiographic evaluation of EAT

The echocardiographic parameters were measured before dialysis using transthoracic examina-

tion in the left lateral decubitus position, including two-dimensional, M-mode, pulsed and color flow Doppler with a GE-Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) machine and a 2.5–3.5 MHz transducer by an experienced cardiologist blinded to other patients' characteristics. During echocardiographic measurement, a single electrocardiogram (lead II) was recorded simultaneously and data were obtained from the average of three cardiac cycles. Standard 2D, M-mode and Doppler calculations were performed in accordance with American Society of Echocardiography guidelines [35]. The Devereux formula [36] was used to calculate left ventricular mass index (LVMI). Epicardial adipose tissue was defined [37] as the echo-free space between the outer wall of the myocardium and visceral layer of the pericardium on the free wall of the right ventricle at the 2D parasternal long-axis view. Epicardial adipose tissue is recognized as hyperechoic and scattered reflection, typically. We measure EAT on magnified M-mode strips obtained from 2D views with longitudinal cursor beam orientation at end diastole. Thickness is perpendicular to the free wall of the right ventricle and the average of three cardiac cycles' measurement is included.

### Statistical analysis

Clinical and experimental data were analyzed using Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for each variable were determined. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation. Results for continuous variables without normal distribution were presented as median (interquartile range (IQR)). A statistically significant difference between the groups was determined by the $\chi^2$ test for categorical variables. Nonparametric statistics (Mann-Whitney *U*) and parametric statistics (independent sample *t* test) were all used for continuous variables. Associations between the variables were explored using Spearman's rho test. Binary logistic regression analysis was also performed to define variables associated with EAT. A statistically significant difference was considered when the *p*-value ≤ 0.05.

## Results

The baseline characteristics of 43 hemodialysis patients (25 females, 18 males; mean age:

**Table I.** Demographic, clinical and laboratory features of the study groups

| Parameters | Healthy subjects (*N* = 30) | HD patients (*N* = 43) | *P*-value |
|---|---|---|---|
| Female/male* | 15/15 | 25/18 | 0.49 |
| Age [years]** | 59.1 ±10.8 | 64.1 ±11.9 | 0.69 |
| BMI [kg/m$^2$]** | 26.7 ±4.9 | 25.8 ±4.6 | 0.42 |
| Duration of hemodialysis [months] | – | 63.3 ±57.1 | – |
| SBP [mm Hg]*** | 115 (107–120) | 130 (120–140) | < 0.001 |
| DBP [mm Hg]*** | 70 (65–76) | 80 (80–90) | < 0.001 |
| Hemoglobin [g/dl]** | 14.3 ±1.7 | 11.2 ±1.8 | < 0.001 |
| Albumin [g/dl]** | 4.2 ±0.2 | 3.58 ±0.3 | < 0.001 |
| Ferritin [ng/ml] | – | 578 (287–1200) | – |
| Calcium [mg/dl] | – | 8.46 ±1.54 | – |
| Phosphorus [mg/dl] | – | 5.00 ±1.55 | – |
| Parathormone [pg/ml] | – | 589 (284–1078) | – |
| CRP [mg/dl]*** | 0.33 (0.22–0.53) | 0.85 (0.44–1.29) | < 0.001 |
| NLR*** | 1.85 (1.57–2.31) | 3.07 (1.78–3.82) | 0.001 |
| EAT [mm]*** | 5.5 (4–7) | 8 (5–10) | 0.001 |
| LVM [g]*** | 85 (79–94) | 208 (193–233) | < 0.001 |
| LVMI [g/m$^2$]*** | 48 (44–54) | 119 (111–139) | < 0.001 |
| EF (%)*** | 67 (65–67) | 64 (60–66) | < 0.001 |

**$\chi^2$, **independent sample t test (mean ± SD), ***Mann-Whitney U test [median (IQR)]. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, CRP – C-reactive protein, NLR – neutrophil-to-lymphocyte ratio, EAT – epicardial adipose tissue, LVM – left ventricular mass, LVMI – left ventricular mass index, EF – ejection fraction.*

**Table II.** Demographic, clinical and laboratory features of HD patients according to NLR groups

| Parameters | NLR < 3.07 (*N* = 21) | NLR ≥ 3.07 (*N* = 22) | *P*-value |
|---|---|---|---|
| Age [years]* | 63.3 ±13.8 | 64.9 ±9.8 | 0.62 |
| BMI [kg/m$^2$]* | 25.2 ±4.4 | 26.4 ±4.9 | 0.40 |
| SBP [mm Hg]** | 135 (120–140) | 130 (120–140) | 0.45 |
| DBP [mm Hg]** | 80 (75–92) | 80 (77–86) | 0.74 |
| Hemoglobin [mg/dl]* | 11.5 ±1.9 | 11 ±1.7 | 0.36 |
| Albumin [g/dl]* | 3.69 ±0.3 | 3.47 ±0.3 | 0.037 |
| Calcium [mg/dl]* | 8.87 ±0.7 | 8.36 ±0.9 | 0.16 |
| Phosphorus [mg/dl]* | 5.3 ±1.5 | 4.82 ±1.6 | 0.44 |
| Parathormone [pg/ml]** | 370 (257–948) | 822 (410–1138) | 0.14 |
| Ferritin [ng/ml]** | 343 (216–574) | 1003 (575–1456) | 0.002 |
| CRP [mg/dl]** | 0.5 (0.3–1.1) | 1 (0.6–1.6) | 0.033 |
| EF (%)** | 64 (60–65) | 62 (60–66) | 0.90 |
| EAT [mm]** | 6 (5–7.5) | 9 (8–11.2) | 0.001 |
| LVM [g]** | 201 (193–235) | 220 (195–233) | 0.42 |
| LVMI [g/m$^2$]** | 115 (112–136) | 119 (108–154) | 0.84 |

**Independent sample t test (mean ± SD), **Mann-Whitney U test [median (IQR)]. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, CRP – C-reactive protein, NLR – neutrophil-to-lymphocyte ratio, EAT – epicardial adipose tissue, LVM – left ventricular mass, LVMI – left ventricular mass index, EF – ejection fraction.*

64.1 ±11.9 years) and 30 healthy control subjects (15 females, 15 males; mean age, 59.1 ±10.8 years) are shown in Table I. The etiology of ESRD patients was diabetic nephropathy ($n$ = 10, 23.3%), chronic glomerulonephritis ($n$ = 4, 9.2%), hypertensive nephropathy ($n$ = 19, 44.2%), polycystic kidney disease ($n$ = 2, 4.7%), nephrolithiasis ($n$ = 4, 9.2%), chronic tubulointerstitial nephritis ($n$ = 2, 4.7%), and unknown ($n$ = 2, 4.7%). There were no significant differences in terms of age, gender and body mass index (BMI) between HD patients and healthy subjects. The healthy control group had significantly lower systolic blood pressure, diastolic blood pressure, EAT, LVM, LVMI, CRP and NLR, while ejection fraction (EF), hemoglobin and albumin levels were significantly higher in this group.

Neutrophil-to-lymphocyte ratio levels were significantly higher in HD patients than in the healthy control group (Table I). HD patients were separated into two groups according to their median value of NLR (group 1, NLR < 3.07 ($n$ = 21) and group 2, NLR ≥ 3.07 ($n$ = 22)). There were no differences with respect to the following variables between these two groups: age, BMI, systolic blood pressure, diastolic blood pressure, EF, LVM, LVMI, serum levels of hemoglobin, calcium, phosphorus and parathormone (Table II). Group 2 patients had significantly higher EAT, CRP and ferritin levels, while albumin levels were significantly lower in this group (Table II). In the bivariate correlation analysis in HD patients, EAT was positively correlated with NLR ($r$ = 0.600, $p$ < 0.001) and ferritin ($r$ = 0.485, $p$ = 0.001) levels.

**Table III.** Predictors of EAT in HD patients

| Parameters | *P*-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| NLR | 0.008 | 3.178 | 1.351 | 7.475 |
| CRP | 0.394 | 0.713 | 0.328 | 1.550 |
| Albumin | 0.563 | 0.342 | 0.009 | 12.919 |
| BMI | 0.164 | 1.157 | 0.942 | 1.420 |

*BMI – body mass index, CRP – C-reactive protein, NLR – neutrophil-to-lymphocyte ratio, EAT – epicardial adipose tissue, CI – confidence interval.*

Binary logistic regression analysis was also performed to define variables associated with EAT (Table III). The BMI, CRP, albumin and NLR levels were included in this model. The NLR levels were found to be an independent predictor of EAT.

## Discussion

There were four main findings of the present study. First, NLR levels were significantly higher in HD patients than in the healthy control group. Second, HD patients who had high inflammatory status were also found to have significantly higher EAT, CRP and ferritin levels and significantly lower serum albumin levels when compared to HD patients with low inflammatory status. Third, in the

bivariate correlation analysis, EAT was positively correlated with NLR in HD patients. Lastly, in the binary logistic regression analysis, NLR levels were found to be independently associated with EAT in these patients. To our knowledge, this is the first study to demonstrate the positive association between EAT and NLR in ESRD patients receiving hemodialysis.

In recent years, researchers have analyzed a large panel of biomarkers to fully characterize the relation between inflammation and CVD, including C-reactive protein, IL-1β, IL-6, and TNF-α in chronic kidney disease and ESRD patients [38–41]. In addition, several interesting new biomarkers were considered to better describe inflammation in this population. In this regard, NLR is a potential marker for inflammation in cardiac and non-cardiac disorders [28, 29, 42] that was also shown to be a predictor of long-term mortality in patients who underwent percutaneous coronary intervention [33]. The authors demonstrated that NLR could predict inflammation in ESRD patients and in renal transplant patients [30, 41]. In accordance with previous studies, in the present study we found that HD patients had higher inflammatory biomarkers including NLR and CRP compared to healthy subjects. Additionally, HD patients who had higher NLR also had higher CRP and ferritin and lower albumin levels.

Epicardial adipose tissue is the true visceral fat depot of the heart that accounts for approximately 20% of total heart weight and covers 80% of the cardiac surfaces, and is mostly in the grooved segments along the paths of coronary arteries [11–13]. Recent studies showed a close relationship between CAD and EAT using MDCT and echocardiography in healthy subjects and patients at a high risk of CAD [14–17]. Although the pathophysiologic role of EAT is not clear to date, the researchers suggest that EAT may act as an extremely active organ that produces several bioactive adipokines as well as proinflammatory and proatherogenic cytokines such as TNF-α, monocyte chemotactic protein (MCP-1), IL-6 and resistin [15, 18–21]. In a recent study, the authors found a relationship between MIAC syndrome and EAT in ESRD patients receiving hemodialysis or peritoneal dialysis [23].

In the present study, among HD patients, those who had higher NLR and CRP also had higher EAT.

This could be attributed to increased inflammatory cytokines that are secreted by EAT in this population. The present study had some limitations. First, this was a cross-sectional analysis of HD patients focusing on the relationship between NLR, CRP and EAT. Second, the sample size was relatively small. Third, since EAT has a three dimensional distribution, two dimensional echocardiographic measurements may not be sufficient to assess the total amount. This was not a prospective controlled study, so we can not draw cause-and-effect relationships from our findings.

In conclusion, the relation between inflammation and adipose tissue is extremely complex in ESRD patients. However, simple calculation of NLR can predict EAT in this population. Taken together, traditional and non-traditional risk factors including chronic low grade inflammation and increased EAT might contribute to cardiovascular disease and the markedly increased mortality in patients with ESRD. Hence, further randomized and controlled studies evaluating the relationship between visceral adipose tissue and NLR in ESRD patients are needed.

## Conflict of interest

The authors declare no conflict of interest.

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