

ORIGINAL ARTICLE

The Association of Neutrophil Lymphocyte Ratio and Glycemic Markers in Hemodialysis Patients

Hemodiyaliz Hastalarında Nötrofil Lenfosit Oranı ve Glisemik Belirteç İlişkisi

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How to cite ?

Topal M. The Association of Neutrophil Lymphocyte Ratio and Glycemic Markers in Hemodialysis Patients. Genel Tıp Dergisi. 2023; 33(4): 466-469.

ABSTRACT

Background/aims: Neutrophil lymphocyte ratio was found as an inflammation marker in the preceding decade and recently related with glycemic indices in patients with diabetes mellitus. The target of this research was to explore the association between neutrophil lymphocyte ratio and glycemic indices in hemodialysis population.

Methods: 177 hemodialysis patients (98 diabetic and 79 non-diabetic) aged 56.08±16.06 years were enrolled in this research. Neutrophil lymphocyte ratio was calculated and its association with predialysis glucose and HbA1c was studied.

Results: NLR was positively correlated with predialysis glucose ($p=0.000$, $r=0.338$), body mass index ($p=0.029$, $r=0.220$), white blood cell ($p=0.000$, $r=0.430$), platelet ($p=0.034$, $r=0.159$), neutrophil ($p=0.000$, $r=0.656$) and C-reactive protein ($p=0.00$, $r=0.377$) levels. In non-diabetic hemodialysis group, predialysis glucose was still correlated with neutrophil lymphocyte ratio ($p=0.047$, $r=0.224$). Diabetics had higher predialysis glucose (185.94 ± 81.11 vs 111.24 ± 25.59 , $p=0.000$) and neutrophil lymphocyte ratio (4.99 ± 4.17 vs 2.82 ± 1.23 , $p=0.000$) compared to non-diabetics.

Conclusion: This study revealed that predialysis glucose levels in hemodialysis patients are correlated with neutrophil lymphocyte ratio and hemodialysis patients with diabetes have higher neutrophil lymphocyte ratio levels. Neutrophil lymphocyte ratio should be recognized as a glycemic control marker along with traditional glycemic indices in HD patients.

Keywords: Diabetes Mellitus, HbA1c, Hemodialysis, Neutrophil Lymphocyte Ratio, Glucose

ÖZ

Amaç: Nötrofil lenfosit oranı son on yılda inflamatuvar bir belirteç olarak ortaya konmuş ve yakın dönemli yayınlarda diyabetik hastalarda glisemik belirteçlerle ilişkili saptanmıştır. Bu çalışmanın amacı hemodiyaliz hastalarında nötrofil lenfosit oranı ve glisemik belirteçlerin ilişkisinin incelenmesidir.

Gereç ve Yöntemler: Çalışmaya yaş ortalaması 56.08±16.06 olan toplam 177 (98 diyabetik ve 79 diyabetik olmayan) hemodiyaliz hastası alınmıştır. Nötrofil lenfosit oranı hesaplanarak prediyaliz glukoz ve HbA1c ile ilişkisi çalışılmıştır.

Bulgular: Nötrofil lenfosit oranı; prediyaliz glukoz ($p=0.000$, $r=0.338$), vücut kitle indeksi ($p=0.029$, $r=0.220$), beyaz küre sayısı ($p=0.000$, $r=0.430$), trombosit sayısı ($p=0.034$, $r=0.159$), nötrofil sayısı ($p=0.000$, $r=0.656$) and C-reaktif protein düzeyleri ($p=0.00$, $r=0.377$) pozitif korelasyon göstermiştir. Diyabetik olmayan grup ayrıca değerlendirildiğinde bile prediyaliz glukoz ile nötrofil lenfosit oranı pozitif korelasyon göstermiştir ($p=0.047$, $r=0.224$). Diyabetik hastaların prediyaliz glukoz düzeyleri (185.94 ± 81.11 vs 111.24 ± 25.59 , $p=0.000$) ile nötrofil lenfosit oranı (4.99 ± 4.17 vs 2.82 ± 1.23 , $p=0.000$) diyabetik olmayanlara göre anlamlı olarak daha yüksek saptanmıştır.

Sonuç: Bu çalışmada hemodiyaliz hastalarında prediyaliz glukoz düzeylerinin nötrofil lenfosit oranı ile korele olduğu ve diyabetik hemodiyaliz hastalarında nötrofil lenfosit oranının daha yüksek olduğu ortaya konmuştur. Hemodiyaliz hastalarında nötrofil lenfosit oranı geleneksel glisemik kontrol belirteçlerine yardımcı bir indeks olarak değerlendirilmelidir.

Anahtar kelimeler: Diyabetes Mellitus, HbA1c, Hemodiyaliz, Nötrofil Lenfosit Oranı, Glukoz

Introduction

The leading reason of chronic renal disease (CRD) is diabetes (1). Glycemic control affects mortality in hemodialysis (HD) patients. HbA1c is recommended as a long term glycemic indicator by guidelines (2,3). Although there are some concerns using HbA1c in diabetic HD patients, it is still the gold standart in dialysis population (4). Neutrophil lymphocyte ratio (NLR) was presented as an inflammation indicator in the preceding decade (5). It has been shown that NLR is related with arteriovenous fistula stenosis (6), cardiovascular events (7), nutrition markers, hospitalization (8), and mortality (9) in HD patients.

NLR was also studied in diabetic patients. Patients who had diabetes mellitus (DM) had higher NLR than non-diabetics (10). It has also been found that it is positively correlated with diabetic microvascular complications (11) and diabetic kidney disease (12,13) in DM patients. Recently, some studies revealed a correlation of NLR with glucose levels both in diabetic and non-diabetic population, and HbA1c in diabetics (14). Nevertheless, HD patients were not investigated under this topic. The target of this research is to explore the relation of NLR and glycemic indicators in HD patients.

Material and Methods

This study was performed between January and April 2022. Ethical approval was obtained from local ethics committee (Date:22.03.2022, Decision number: E-41901325-200-30572-38), and has been performed in compliance with the Helsinki declaration. 177 subjects experiencing HD at least for 3 months were included in this research. Patients who were under 18 years old, who had signs of active infection, who undergone major surgery, who had active hemorrhage or had blood transfusion in last 3 months were excluded. Anthropometric measures of patients were utilized to assess body mass index (BMI) as kg/m². Patient characteristics like age, sex and HD vintage were noted. Serum glucose, calcium, phosphorus, albumin, ferritin, parathormone (PTH), LDL cholesterol (LDL-C), triglyceride (TG), C-reactive protein (CRP) and complete blood cell, derived parameters such as hemoglobin (Hb), white blood cell (WBC), thrombocyte, neutrophil and lymphocyte counts were measured using automated and standardized methods. They were obtained predialysis as a part of monthly laboratory tests. NLR was determined as simple division of neutrophil to lymphocyte count. HbA1c was measured in diabetic patients by Arkray ADAMS HA-8180V system.

SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA.) for Windows version 22 was used for computing the statistical analysis. After Kolmogorov-Smirnov normality test, correlation was done by Pearson test for parametric and Spearman test for non-parametric variables. Mann-Whitney U test was applied for non-parametric variables. A p value of <0.05 was considered statistically significant.

Results

177 HD patients were included in this study. 98 (%55.4) were diabetic and 91 (%51.4) were men. Mean age of the individuals was 56.08±16.06 years. Some patient characteristics are shown in table 1. NLR was positively correlated with predialysis glucose (PG) (p=0.000, r=0.338), BMI (p=0.029, r=0.220), WBC (p=0.000, r=0.430), thrombocyte (p=0.034, r=0.159), neutrophil (p=0.000, r=0.656) and CRP (p=0.00, r=0.377) levels. NLR was inversely correlated with albumin (p=0.000, r=-0.296) and lymphocyte count (p=0.000, r=-0.501). HbA1c levels were positively correlated with PG (p=0.000, r=0.693), BMI (p=0.011, r=0.220) and CRP (p=0.027, r=0.223) levels. PG levels were positively correlated with NLR (p=0.000, r=0.338) (figure 1), HbA1c (p=0.000, r=0.693), WBC (p=0.002, r=0.227), neutrophil (p=0.000, r=0.288) and CRP (p=0.009, r=0.195) levels. PG was inversely correlated with albumin (p=0.000, r=-0.277) levels. In non-diabetic HD group PG was still correlated with NLR (p=0.047, r=0.224). Diabetics were older (62.81±12.32 vs 47.73±16.30, p=0.000), had higher BMI (27.50±5.56 vs 23.88±4.03, p=0.001), PG (185.94±81.11 vs 110.76±25.56, p=0.000), WBC (8.19±2.85 vs 7.44±3.28, p=0.026), platelet (237.70±77.51 vs 201.34±74.80, p=0.000), neutrophil (5.97±2.51 vs 4.76±2.40, p=0.000), NLR (4.99±4.17 vs 3.60±4.18, p=0.000), LDL-C

(101.04±34.87 vs 86.85±27.21, p=0.004) and lower albumin (3.82±0.39 vs 4.06±0.40, p=0.000) levels (table 2). Diabetic and non-diabetic groups were not found different in terms of gender, Hb or CRP levels. After grouping diabetic HD patients according to HbA1c as <7 and ≥7, there was still no significant relation with NLR.

Table 1: Patient characteristics.

Parameter	Mean value or %
Age (years)	56.08±16.06
Gender (female)	86 (%48.6)
Diabetes mellitus (n)	98 (%55.4)
Predialysis glucose (mg/dl)	152.38±72.93
HbA1c (%)	6.94±1.50
WBC (10 ⁹ /μL)	7.86±3.06
Neutrophil count (10 ⁹ /μL)	5.43±2.53
Lymphocyte count (10 ⁹ /μL)	1.51±0.61
Uric acid (mg/dl)	6.18±1.45
Albumin (g/l)	3.93±0.41
Ferritin (μg/l)	578.91±452.97
C reactive protein (mg/l)	14.03±23.44
Parathormone (μg/l)	426.17±391.50
LDL cholesterol (mg/dl)	178.50±94.76
Triglyceride (mg/dl)	183.17±107.93

Table 2: Statistically significant differences between diabetic and non-diabetic HD patients.

Parameters	Diabetics	Non-diabetics	p value
Age (years)	64.5 (21-87)	48 (19-80)	0.000
BMI (kg/m ²)	27.33 (14.67-41.72)	23 (17-32)	0.001
Predialysis glucose (mg/dl)	167 (77-514)	104 (70-196)	0.000
WBC (10 ⁹ /μL)	7.48 (4.2-18.5)	6.67 (3.1-25.1)	0.026
Platelet (10 ⁹ /μL)	238 (62-458)	193 (55-413)	0.000
Neutrophil (10 ⁹ /μL)	5.36 (2.10-14.96)	4.04 (1.58-15)	0.000
NLR	3.81 (1.04-26.45)	2.55 (1.09-35.94)	0.000
LDL cholesterol(mg/dl)	103.55 (40-178.5)	86 (35-156)	0.004
Albumin (g/l)	3.9 (2.7-4.5)	4.1 (2.6-5.1)	0.000

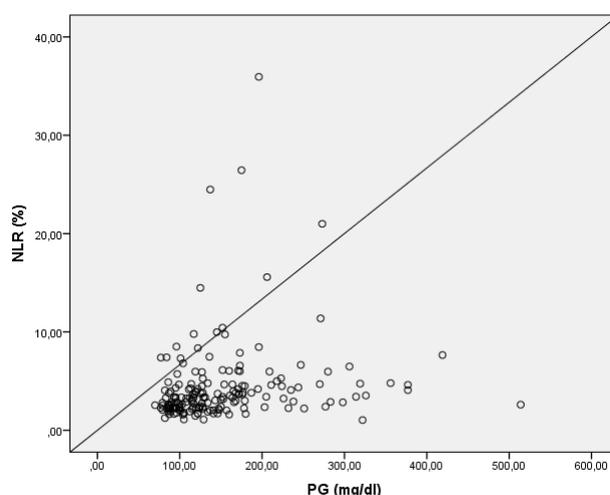


Figure 1: Correlation of predialysis glucose with neutrophil lymphocyte ratio (p=0.000, R=0.338).

Discussion

This study showed that NLR was higher in HD patients who had DM than non-diabetics. Moreover, there was also a positive correlation of NLR and PG levels even in the non-diabetic HD group.

Shiny et al. (15) demonstrated that NLR of diabetics were higher than control group. Besides, NLR was positively correlated with both HbA1c and blood glucose levels. This was the first research to show a relation between both glucose and HbA1c and NLR. In the research of Sefil et al. (16) 71 patients with DM were studied. Two groups were designed according to HbA1c levels. NLR was found to have increased in the HbA1c ≥ 7 group.

330 diabetic patients were grouped as excellent, poor and worst control according to HbA1c levels in the study of Hussain et al. (17). They found that the worst control group had a significantly higher NLR and NLR was also found as an independent predictor of worst control.

278 individuals were divided as normoglycemic and hyperglycemic in the study of Mendes et al (18). No significant difference was revealed in terms of NLR and even in the hyperglycemic patients after grouping according to HbA1c as < 7 and ≥ 7 .

77 patients with DM and 33 control were studied by Duman et al. (14). Diabetics had an increased NLR compared to controls. NLR was also correlated with HbA1c and glucose levels. 130 diabetic men's NLR were studied by Bilgin et al. (19). They found a positive correlation between NLR and HbA1c.

There are other studies revealing that NLR is higher in patients with DM compared to control (20,21). Lou et al. also showed that insulin resistance and NLR were correlated.

The relation of NLR with serum glucose was investigated at admission in individuals with spontaneous intracerebral hemorrhage (22). Zhang et al. showed a positive correlation between NLR and glucose in a mixed group of diabetic and non-diabetic 175 patients.

Overall, the general literature confirms that NLR is related with HbA1c and glucose, and NLR increases in diabetics. Nevertheless, none of the researches above included HD patients. This study revealed that NLR was higher in diabetic hemodialysis patients and NLR was correlated with PG levels. These findings are consistent with general literature. However, NLR and HbA1c were not correlated in diabetic HD patients. HbA1c is a part of Hb A and is therefore, affected by anemia. Anemia –primarily due to inadequate synthesis of erythropoietin- is a frequent complication of CRD. Besides, there are some other factors affecting Hb levels in CRD patients like deficiencies in iron, vitamin B12 and folate or anemia treatment with iron and erythropoietin stimulating agents (4). All these factors may result in over or underestimation of HbA1c in HD patients. The complicated relation of anemia and its

treatment over HbA1c in HD patients may explain the findings in this study.

Other than this, the primary limitation of this current research may be the size of the participants. More populated patient groups may produce a better result of the relation of NLR and HbA1c in HD patients. However, as far as is known, this is the first study to examine the relationship between NLR and glycemic indices in HD patients.

In conclusion, this study has demonstrated that glucose levels in HD patients are correlated with NLR, and HD patients with DM have higher NLR levels compared to non-diabetic HD patients. NLR should be recognized as a marker of glucose control along with traditional glycemic indices in HD patients. Further studies are warranted to verify this result.

Ethical Declarations

Ethics Committee Approval: The study was initiated with the approval of the local ethics committee presidency (Date:22.03.2022, Decision number: E-41901325-200-30572-38).

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

References

- Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. *Diabetes Care* 2009 Jul;32,7:1320-6. doi: 10.2337/dc08-0779.
- Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020 Oct;98,4S:S1-S115. doi: 10.1016/j.kint.2020.06.019.
- American Diabetes Association Professional Practice Committee; American Diabetes Association Professional Practice Committee; Draznin B, Arora VR, Bakris G, Benson G, Brown FM, Freeman R, et al. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022 Jan 1;45,Supplement_1:S83-S96. doi: 10.2337/dc22-S006.
- Copur S, Onal EM, Afsar B, Ortiz A, van Raalte DH, Cherney DZ, et al. Diabetes mellitus in chronic kidney disease: Biomarkers beyond HbA1c to estimate glycemic control and diabetes-dependent morbidity and mortality. *J Diabetes Complications* 2020 Nov;34,11:107707. doi: 10.1016/j.jdiacomp.2020.107707.
- Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. *Am J Emerg Med* 2020 Mar;38,3:641-7. doi: 10.1016/j.ajem.2019.10.023.
- Yilmaz H, Bozkurt A, Cakmak M, Celik HT, Bilgic MA, Bavbek N, et al. Relationship between late arteriovenous fistula (AVF) stenosis and neutrophil-lymphocyte ratio (NLR) in chronic hemodialysis patients. *Ren Fail* 2014 Oct;36,9:1390-4. doi: 10.3109/0886022X.2014.945183.
- Zhu X, Li G, Li S, Gong Z, Liu J, Song S. Neutrophil-to-lymphocyte ratio and red blood cell distribution width-to-platelet ratio predict cardiovascular events in hemodialysis patients. *Exp Ther Med* 2020 Aug;20,2:1105-1114. doi: 10.3892/etm.2020.8756.
- Diaz-Martinez J, Campa A, Delgado-Enciso I, Hain D, George F, Huffman F, et al. The relationship of blood neutrophil-to-lymphocyte ratio with nutrition markers and health outcomes in hemodialysis patients. *Int Urol Nephrol* 2019 Jul;51,7:1239-1247. doi: 10.1007/s11255-019-02166-6.
- Catabay C, Obi Y, Streja E, Soohoo M, Park C, Rhee CM, et al.

Lymphocyte Cell Ratios and Mortality among Incident Hemodialysis Patients. *Am J Nephrol* 2017;46,5:408-416. doi: 10.1159/000484177.

10.Mertoglu C, Gunay M. Neutrophil-Lymphocyte ratio and Platelet-Lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. *Diabetes Metab Syndr* 2017 Nov;11 Suppl 1:S127-S131. doi: 10.1016/j.dsx.2016.12.021.

11.Fawwad A, Butt AM, Siddiqui IA, Khalid M, Sabir R, Basit A. Neutrophil-to-lymphocyte ratio and microvascular complications in subjects with type 2 diabetes: Pakistan's perspective. *Turk J Med Sci* 2018 Feb 23;48,1:157-161. doi: 10.3906/sag-1706-141.

12.Huang W, Huang J, Liu Q, Lin F, He Z, Zeng Z, et al. Neutrophil-lymphocyte ratio is a reliable predictive marker for early-stage diabetic nephropathy. *Clin Endocrinol (Oxf)* 2015 Feb;82,2:229-33. doi: 10.1111/cen.12576.

13. Kawamoto R, Ninomiya D, Kikuchi A, Akase T, Kasai Y, Kusunoki T, et al. Association of neutrophil-to-lymphocyte ratio with early renal dysfunction and albuminuria among diabetic patients. *Int Urol Nephrol* 2019 Mar;51,3:483-490. doi: 10.1007/s11255-018-02065-2.

14.Duman TT, Aktas G, Atak BM, Kocak MZ, Erkus E, Savli H. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. *Afr Health Sci* 2019 Mar;19,1:1602-6. doi: 10.4314/ahs.v19i1.35.

15.Shiny A, Bibin YS, Shanthirani CS, Regin BS, Aniana RM, Balasubramanyam M, et al. Association of neutrophil-lymphocyte ratio with glucose intolerance: an indicator of systemic inflammation in patients with type 2 diabetes. *Diabetes Technol Ther* 2014 Aug;16,8:524-30. doi: 10.1089/dia.2013.0264.

16.Sefil F, Ulutas KT, Dokuyucu R, Sumbul AT, Yengil A, Yagiz AE, et al. Investigation of neutrophil lymphocyte ratio and blood glucose regulation in patients with type 2 diabetes mellitus. *J Int Med Res* 2014 Apr;42,2:581-8. doi: 10.1177/0300060513516944.

17.Hussain M, Babar MZM, Akhtar L, Hussain MS. Neutrophil lymphocyte ratio (NLR): A well assessment tool of glycemic control in type 2 diabetic patients. *Pak J Med Sci* 2017 Nov-Dec;33,6:1366-1370. doi: 10.12669/pjms.336.12900.

18.Mendes BB, Oliveira ACR, Alcântara KC. Comparison of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in normoglycemic and hyperglycemic subjects. *Einstein (Sao Paulo)* 2019 Jan 14;17,1:eAO4403. doi: 10.31744/einstein_journal/2019AO4403.

19.Bilgin S, Aktas G, Zahid Kocak M, Atak BM, Kurtkulagi O, Duman TT, et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. *Aging Male* 2020 Dec;23,5:923-7. doi: 10.1080/13685538.2019.1632283. Epub 2019 Jun 28.

20.Demirtas L, Degirmenci H, Akbas EM, Ozcicek A, Timuoglu A, Gurel A, et al. Association of hematological indices with diabetes, impaired glucose regulation and microvascular complications of diabetes. *Int J Clin Exp Med* 2015 Jul 15;8,7:11420-7.

21.Lou M, Luo P, Tang R, Peng Y, Yu S, Huang W, et al. Relationship between neutrophil-lymphocyte ratio and insulin resistance in newly diagnosed type 2 diabetes mellitus patients. *BMC Endocr Disord* 2015 Mar 2;15:9. doi: 10.1186/s12902-015-0002-9.

22.Zhang F, Ren Y, Fu W, Wang Y, Qian J, Tao C, et al. Association between neutrophil to lymphocyte ratio and blood glucose level at admission in patients with spontaneous intracerebral hemorrhage. *Sci Rep* 2019 Oct 30;9,1:15623. doi: 10.1038/s41598-019-52214-5.