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ARAŞTIRMA / RESEARCH

Relationship between mortality and baseline platelet to lymphocyte ratio in hemodialysis patients

Hemodiyaliz hastalarında mortalite ile bazal trombosit lenfosit oranı arasındaki ilişki

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Abstract

Purpose: The aim of this study was to evaluate baseline parameters including platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) as predictive value for mortality in hemodialysis patients.

Materials and Methods: In this study 129 patients undergoing hemodialysis more than 3 months, were evaluated for survival between 1999 and 2017. In the 3. Month of beginning of hemodialysis clinical and laboratory parameters of the patients were evaluated retrospectively. The patients were separated into 2 groups as dead and living. After 30 excluded patients due to study criteria, 33 paients of the remaining 99 patients died and 66 were still undergoing hemodialysis.

Results: The mean age of patients was 57 ± 18.9 years (13-93), 46.5% (46) were female and mean hemodialysis vintage was 35.02 ± 30.44 months. According to Kaplan Meier, survival analysis PLR was significantly higher in hemodialysis patients who died compared to surviving hemodialysis patients but NLR was not different in hemodialysis patients who surviving or died. Multivariate Cox regression analysis model, correlated factors associated with mortality were PLR and serum sodium.

Conclusion: Baseline PLR and serum sodium were found to be sensitive biomarkers for mortality. Baseline 3. hemodialysis month PLR of which is easily accessible, inexpensive and simple, can be a predictor of mortality at follow up period in hemodialysis patients.

Keywords: End stage renal failure, hemodialysis, platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, mortality

Öz

Amaç: Bu çalışmada, hemodiyaliz hastalarında trombosit-lenfosit oranı (PLR) ve nötrofil-lenfosit oranı (NLR) gibi temel parametrelerin mortalite ile ilişkisinin değerlendirilmesi amaçlanmıştır..

Gereç ve Yöntem: Bu çalışmada, 1999-2017 yılları arasında, 3 aydan uzun süre hemodiyalize giren 129 hasta retrospektif olarak değerlendirildi. Hastalar dışlama kriterlerinden sonra, halen diyalize giren (n=66) ve ölen (n=33) olarak 2 gruba ayrıldı. Hastaların hemodiyaliz başlangıç (hemodiyalizden sonraki üçüncü ay) klinik ve laboratuvar kayıtları değerlendirilerek mortalite ile ilişkisi araştırıldı.

Bulgular: Hastaların yaş ortalaması 57 ± 18,9 yıl (13-93), % 46,5'i (46) kadın ve ortalama hemodiyaliz süresi 35.02 ± 30.44 ay idi. Kaplan Meier sağkalım analizine göre PLR, sağ kalan hemodiyaliz hastalarına kıyasla ölen hemodiyaliz hastalarında anlamlı olarak daha yüksekti, ancak NLR sağ kalan ya da ölen hemodiyaliz hastalarında farklı değildi. Çok değişkenli Cox regresyon analiz modelinde, mortalite ile ilişkili faktörler PLR ve serum sodyum idi.

Sonuç: Bazal PLR ve serum sodyumun mortalite için hassas biyobelirteçler olduğunu söyleyebiliriz. Hemodiyalizin 3. ayındaki bazal PLR, kolay erişilebilir, ucuz ve basit bir belirteç olup takip süresince mortalite göstergesi olabilir.

Anahtar kelimeler: Son dönem böbrek yetmezliği, hemodiyaliz, trombosit-lenfosit oranı, nötrofil-lenfosit oranı, mortalite

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INTRODUCTION

Cardiovascular disease (CVD) is the major cause of mortality in patients with end-stage renal disease (ESRD), and their mortality rates are 10 to 20 times higher than the normal population[1]. In patients with chronic renal disease (CKD) in addition to traditional atherosclerotic risk factors such as advanced age, hypertension (HT), dyslipidemia, diabetes mellitus (DM), smoking; inflammation, oxidative stress, endothelial dysfunction, vascular calcification, malnutrition are also associated with cardiovascular mortality[2,3]. Persistent inflammation in patients with CKD also plays a role in the protein-energy wasting, malnutrition, anemia, bone-mineral disorders, and malnutrition-inflammation atherosclerosis (MIA) syndrome as well as CVD involving early atherosclerosis (AS)[3,4].

Impaired renal elimination of cytokines, oxidative stress, metabolic acidosis, vitamin D deficiency, uremic toxins, and intestinal dysbiosis are responsible for the inflammation in CKD patients[4,5]. In addition to an inflammatory condition in patients with CKD, hemodialysis-related factors such as catheter-related infections, vascular access infections, thrombotic arteriovenous fistula (AVF) and grafts, bio-incompatible membranes, non-sterile dialysis fluids also contribute to inflammation in hemodialysis (HD) patients[4-6]. Inflammatory biomarkers such as C reactive protein (CRP) and interleukin-6 (IL-6) are associated with mortality in ESRD patients[7-9].

In systemic inflammatory conditions, significant changes occur in the blood components of neutrophils, lymphocytes, and platelets. Proinflammatory cytokines such as IL-1 and IL-6 induce thrombocytosis by stimulating proliferation of megakaryocytes[10-12]. Lymphocytopenia is seen due to increased margination, redistribution, and apoptosis. In contrast, neutrophilia developes secondary to delayed apoptosis, stem cell stimulation by growth factors during systemic inflammation[13].

The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) are cheap, easily accessible, and increasingly becoming widespread systemic inflammatory biomarkers. Recently, the prognostic significance of NLR and PLR are gradually increased in various diseases such as CKD, malign diseases, cardiac diseases, autoimmune diseases and pneumonia[14-17]. It is known that inflammation in HD patients with ESRD contributes to increased mortality rates[18,19]. The association between mortality and PLR, NLR is still unclear in HD patients. In this study, we evaluated the correlation between mortality and the basal PLR and NLR values of 99 HD patients.

MATERIALS AND METHODS

In this retrospective study 129 patients undergoing hemodialysis more than 3 months in hemodialysis center of Osmaniye State of Hospital, were evaluated for survival between 1999 and 2017. All patients were treated with standard bicarbonate solution and high flux dialyzer for 4 hours x 3 times in a week. The blood tests of the patients were taken in the middle of the week, at the third month after the dialysis starts. Thirty patients with active infection, malignant disease, acute MI, acute heart failure, connective tissue disease were excluded from this study (**Figure 1**). Demographic characteristics of patients were recorded. At the 3. month after the HD beginning (baseline) biochemical and hematological parameters including complete blood count, NLR, PLR, blood urea nitrogen (BUN), creatinine, uric acid, albumin, corrected calcium (Ca), phosphorus (P), CaXP, parathormone (PTH), sodium (Na), CRP, ferritin, Transferrin saturation, bicarbonate, cholesterol, triglycerides were recorded. Demographic and laboratory parameters of the patients were compared according to surviving (99) or dead (33) and the median values of PLR and NLR.

Informed consent was obtained from all surviving study patients. Demographic and laboratory data of the patients were obtained hemodialysis files. Hemodialysis patient files are properly and completely protected in dialysis unit, because data can be audited by the insurance or health ministry when necessary. This study has been approved by the ethics committee of the Cukurova University Faculty of Medicine (31.08.2018, 80/32).

Biochemical measurements

Biochemical parameters were measured by enzymatic colorimetric assay on automated clinical chemistry analyzers (Roche/Hitachi 912/917/MODULAR: CAN 525; Roche Diagnostics). Serum ferritin was measured by the immunoturbidimetric method (Roche Diagnostics, Indianapolis, IN) in a Roche/Hitachi Modular analyzer. CRP was measured using the immunoturbidimetric method in a Date Behring BN II device and HbA1c was measured

using the immunoturbidimetric method in a Roche Integra 800 device. PTH was measured using the electro chemoluminescence technique in a Roche Elecys -170 device and 25 OH Vitamin D was measured in an using HPLC (High-pressure liquid chromatography) in Agilent-1100 device. The complete blood count was measured using a Beckman Coulter LH 780. NLR and PLR were calculated by dividing the number of neutrophils and platelets in circulating lymphocytes.

Statistical analysis

The distribution of the values of experimental variables was evaluated for normality visually in histograms and probability plots and analytically by the Kolmogorov–Smirnov test. Differences between groups were analyzed using Chi-square, Mann-Whitney U and Student *t* tests. Univariate analysis was used to determine the relationships between NLR and PLR and other variables. Correlations were determined with the Pearson test for normally distributed data and the Spearman Rank correlation test for nonparametric data. All-cause mortality rates were determined by Kaplan-Meier analysis and compared using the log-rank test. Univariate Cox proportional hazards regression analysis was performed to identify variables associated with mortality; multivariate analysis included variables that were associated with mortality in univariate analysis. A P-value of 0.05 was considered significant. All statistical analyses were performed using Statitiscal Package for the Social Sciences (SPSS) for Windows 21.0 software (SPSS Inc., Chicago, IL, USA). Analysis was made with G * Power 3.0.10 program

RESULTS

The basal demographic characteristics and laboratory results of the patients are shown in Table 1. The median values of NLR and PLR were 3.2 (range 1,3-9,3) and 137.2 (range 33-460), respectively. The causes of death of the patients were cardiovascular diseases 19 (57.6%), infection 4 (12.1%), malignancy 4 (12.1%), cerebrovascular event 4 (12.1%) and other causes 2(6.1%) (Figure 2).

When patients were dividing according to NLR ≥ 3.2 and NLR < 3.2 and PLR ≥ 137.2 and PLR < 137.2 gender, BMI, medicatons, primer renal disease, serum levels of BUN, creatinine, uric acid, calcium, phosphorus, bicarbonate and lipids were similar respectively. Cut-of value were calculated as 3.2 and 137.2 for NLR and PLR respectively. Comparisons of hemodialysis parameters and laboratory values according to cut-of values of PLR and NLR were shown in the Table 2 and 3. .

Comparing to NLR > 3.2 in NLR < 3.2 group, WBC (P < 0.001), neutrophil count (P<0.001), PLR (P=0.001), CRP (P=0.051) values were lower and serum sodium (P = 0.054) and lymphocyte count (P<0.001) were higher. Serum calcium (P=0.025), CRP (P=0.047), NLR (P=0.002), platelet count (P<0.001) and mortality (P=0.033) were lower in the group with PLR < 137.2, while serum lymphocyte count (P<0.001) and albumin (P=0.030) were higher. The basal demographic, clinical and biochemical characteristics of dead and living patients are shown in Table 4. PLR (P=0.023) and weekly UF (P=0.049) of dead HD patients were found to be higher and serum sodium (P=0.020) and lymphocyte levels (P=0.005) were lower. Correlations between biochemical tests and NLR, and PLR are shown in Table 5.

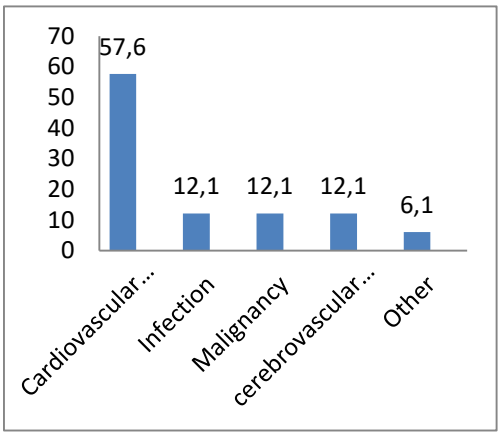

Figure 2. The causes of death in patients (n: 33,%).

In Kaplan Meier survival analysis, patients with higher PLR had a significantly higher mortality rate than those with lower PLR (P=0.002) (Figure 3), whereas there was not a significant survival difference between the two groups with NLR<3.2 and ≥3.2 (P=0.07) (Figure 4). Whilst in the Univariate Cox regression analysis model, factors associated with mortality due to all causes were serum albumin (P=0.041), serum sodium (P=0.008) and PLR (P=0.004), in the multivariate Cox regression analysis model, correlated factors were PLR (P=0.029) and serum sodium (P=0.003) (Table 6). The power of the study was 'Post Hoc Power: 0.886' for NLR and 'Post Hoc Power: 1,000' for PLR.

Table 1. Demographic characteristic and laboratory measurements of patients

Variable	N (%) or mean±SD
Age (years)	57 ± 18.9
Gender (n/ %)	99/100
Female	46/46.5
Male	53/53.5
BMI (kg/m2)	19.6 ± 4.9
Etiology of CKD n, (%)	99/100
DM	49/49.5
HT	13/13.1
Chronic GN	9/9.1
PKD	3/3
Unknown	21/21.2
Other known cause	4/4
Medications	
Erythropoietin, IU/week	5626 ± 3394
Iron sucrose, IV, mg/month	196 ± 139
Calcitriol, n(%)	36 (36.4)
Phosphate binders, n(%)	60 (60.6)
Beta Blocker, n(%)	35(35,4)
Calcium Channel Blocker, n(%)	25(25,3)
ACE Inhibitor or ARB, n(%)	3(3)
Alpha Blocker, n(%)	10 (10.1)
Carnitine IV, n(%)	25 (25.3)
Essential amino acid, n(%)	17 (17.2)
Duration of HD (months)	35.02 ± 30.44
Vascular access type *n*, (%)	99/100
AV fistula	77/77.8
Permanent catheter	22/22.2
SBP (mmHg)	128.9 ± 16.3
DBP(mmHg)	75.7 ± 8.8
KT/V	1.35 ± 0.22
UF (ml/kg/h)	21.8 ± 10.9
BUN (mg/dL)	62.5 ± 21.6
Creatinine (mg/dL)	7.3 ± 2.4
Uric acid (mg/dL)	6.4 ± 1.4
Na (mmol/L)	137 ± 3.5
Calcium (mg/dL)	8.7 ± 1.01
Phosphorus (mg/dL)	5.0 ± 1.5
CaxP (mg2/dL2)	42.9 ± 13.3
Albumin (g/dL)	3.7 ± 0.49
CRP (mg/dL)	7.9 (0.1-193)
WBC × 10^3 (mm^3)	7.8 ± 3.0
Ferritin (ng/mL)	447 ± 341
Neutrophils (mm^3)	5560 ± 2660
Lymphocytes (mm^3)	1614 ± 450
Hemoglobin (g/dL)	10.6 ± 1.6
NLR (median)	3.2 (1.3-9.3)
Transferrin saturation (%)	28 ± 13.6
Platelets × 10^3 (mm3)	223 ± 79
PLR (median)	137.2 (33-460)
Bicarbonate (mEq/L)	18,4 ± 1,6
PTH (pg/mL)	343 ± 299
T. Cholesterol (mg/dL)	159 ± 38.7
LDL Cholesterol (mg/dL)	90.4 ± 35.5

HDL Cholesterol (mg/dL)	36.8 ± 12.5
Triglycerides (mg/dL)	176 ± 106

NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; CKD = chronic kidney disease; CRP = C-reactive protein; PTH = parathyroid hormone; UF = ultrafiltration; SBP = systolic blood pressure; DBP = diastolic blood pressure; GN = glomerulonephritis; WBC = white blood cell.

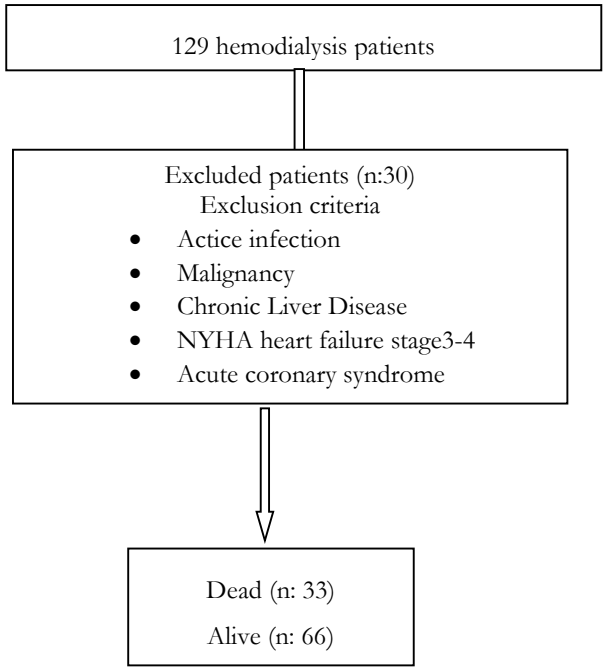

Figure 1. Diagram of patients according to exclusion criteria

Table 2. Demographic and biochemical characteristics of the study population based on NLR

Parameters	**NLR < 3.2 (n: 46)**	**NLR ≥ 3.2 (n: 53)**	**P-value**
Age (years)	56.1 ± 20.2	58.3 ± 17.8	0.578
Duration of HD (months)	37.6 ± 30,8	32.8 ± 30.2	0.438
Vascular access type n, (%)			0.914
AV fistula	36	41	
Permanent catheter	10	12	
SBP (mmHg)	127.4 ± 15.4	130.4 ± 17.1	0.367
DBP(mmHg)	75.2 ± 7.8	76.0 ± 9.7	0.648
Kt/V	1.38 ± 0.25	1.33 ± 0.19	0.306
UF (ml/kg/h)	21.6 ± 10,5	23.1 ± 11.2	0.546
Death, n(%)	11 (33.3)	22 (66.7)	0.087
Na (mmol/L)	137.8 ± 3.3	136.4 ± 3.6	0.054
Calcium (mg/dL)	8.7 ± 0.73	8.6 ± 1.22	0.469
CaxP (mg2/dL2)	41.9 ± 14.7	43.8 ± 12	0.469
Albumin (g/dL)	3.8 ± 0.42	3.7 ± 0.53	0.279
CRP (mg/dL)	12.0 (0.4-59)	23.7 (0,1-193)	0.051
WBC × 10^3 (mm^3)	6.4 ± 1.7	9.1 ± 3.3	< 0.001
Ferritin (ng/mL)	464 ± 338	432 ± 346	0.650
Neutrophils (mm^3)	4059 ± 1014	6866 ± 2951	< 0.001
Lymphocytes (mm^3)	1772 ± 369	1477 ± 472	< 0.001
Hemoglobin (g/dL)	10.6 ± 1.5	10.4 ± 1.6	0.551

NLR	2.35 (1.3-3.1)	4 (3.2–9.3)	< 0.001
Platelets × 10^3 (mm^3)	216 ± 79	230 ± 79	0.393
PLR	119.7 (33-238)	156.(60-460)	0.001
PTH (pg/mL)	325 ± 311	359 ± 289	0.574

NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; CKD = chronic kidney disease; CRP = C-reactive protein; PTH = parathyroid hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3. Demographic and biochemical characteristics of the study population based on PLR

Parameters	**PLR < 137.2 (n: 49)**	**PLR ≥ 137.2 (n: 50)**	**P-value**
Age (years)	56.8 ± 19.7	57.7 ± 18.2	0.830
Duration of HD (months)	40.3 ± 34.2	29.8 ± 25.5	0.086
Vascular access type (*n*), (%)			0.957
AV fistula	38	39	
Permanent catheter	11	11	
SBP (mmHg)	130 ± 14.4	128 ± 18	0.545
DBP(mmHg)	76.6 ± 7.9	74.7 ± 9.7	0.280
KT/V	1.36 ± 0.21	1.35 ± 0.24	0.805
UF (ml/kg/h)	23.5 ± 12.1	21.7 ± 9.6	0.408
Death, n(%)	11 (33.3)	22.(66.7)	0.033
Na (mmol/L)	137.7 ± 3.4	136.4 ± 3.5	0.064
Calcium (mg/dL)	8.4 ± 1.2	8.8 ± 0.8	0.025
CaxP (mg2/dL2)	41.2 ± 12.9	44.6 ± 13.6	0.208
Albumin (g/dL)	3.8 ± 0.4	3.6 ± 0.5	0.030
CRP (mg/dL)	6.4 (0.1-149)	24.1 (0.5-193)	0.047
WBC × 10^3 (mm^3)	7.6 ± 2,4	8.1 ± 3.5	0.493
Ferritin (ng/mL)	480 ± 393	415 ± 281	0.348
Neutrophils (mm3)	5324 ± 2128	5794 ± 3098	0.383
Lymphocytes (mm^3)	1786 ± 357	1446 ± 472	< 0.001
Hemoglobin (g/dL)	10.8 ± 1.5	10.3 ± 1.6	0.151
NLR	2,35 (1.3-3.1)	4 (3.2-9.3)	0.002
Platelets × 10^3 (mm^3)	216 ± 79	230 ± 79	< 0.001
PLR	98.3 (33-136)	184 (137-460)	< 0.001
PTH (pg/mL)	374 ± 315	312 ± 281	0.308

NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; CKD = chronic kidney disease; CRP = C-reactive protein; PTH = parathyroid hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 4. Demographic, clinical and biochemical characteristics of dead and living patients

Parameters	**Alive undergoing Dialysis (n: 66)**	**Exitus (n:33)**	**P-value**
Age (years)	56.4 ± 17.8	59 ± 20.9	0.887
Gender (*n*/ %)	66/100	33/100	0.778
Female	30/45.5	16/48.5	
Male	36/54.5	17/51.5	
BMI (kg/m2)	20.5 ± 4.9	17.6 ± 4.3	0.391
Etiology of CKD *n*, (%)	66/100	33/100	0.039
DM	35/53	14/42.4	
HT	6/9.1	7/21.2	
Chronic GN	4/6.1	5/15.2	
PKD	2/3	1/3	
Unknown	18/27.3	3/9.1	
Other known cause	1/1.5	3/3	
Duration of HD (months)	34.3 ± 27.8	36.3 ± 35.6	0.298
Vascular access type *n*, (%)	66/100	33/100	0.736

AV fistula	52/78.8	25/75.8	
Permanent catheter	14/21.2	8/24.2	
SBP (mmHg)	130.6 ± 14.7	125.8 ± 18.8	0.203
DBP(mmHg)	76.6 ± 7.4	73.8 ± 11.1	0.096
KT/V	1.37 ± 0.23	1.33 ± 0.20	0.400
UF (ml/kg/h)	20.9 ± 21.7	25.8 ± 12.3	0.049
BUN (mg/dL)	61.4 ± 22.1	64.7 ± 20.6	0.470
Creatinine (mg/dL)	7.6 ± 2.5	6.5 ± 2.2	0.941
Uric acid (mg/dL)	6.7 ± 1.4	6,0 ±1,3	0.329
Na (mmol/L)	137.8 ± 3	135.5 ± 4	0.020
Calcium (mg/dL)	8.6 ± 0.7	8.7 ± 1.5	0.533
Phosphorus (mg/dL)	4.8 ± 1.4	5.3 ± 1.5	0.505
CaxP (mg2/dL2)	41.6 ± 13	45.6 ± 14	0.533
Albumin (g/dL)	3.8 ± 0.4	3.6 ± 0.6	0.349
CRP (mg/dL)	7(0.4-85)	8.6(0.1-193)	0.113
WBC × 103 (mm3)	7.6 ± 1.9	8.4 ± 4.4	0.781
Ferritin (ng/mL)	357 ± 186	628 ± 486	0.467
Neutrophils (mm3)	5176 ± 1511	6333 ± 4013	0.437
Lymphocytes (mm3)	1729 ± 403	1385 ± 457	0.005
Hemoglobin (g/dL)	10.7 ± 1.4	10.1 ± 1.8	0.065
NLR	3 (1.3-9)	4.7 (1.6–9.3)	0.065
Transferrin saturation (%)	28.9 ± 12.3	34.2 ± 15.5	0.626
Platelets × 103 (mm3)	216 ± 77	238 ± 82	0.232
PLR	124.6 (33-460)	181.8 (75-442)	0.023
Bicarbonate (mEq/L)	18.6 ± 1.6	18.1 ± 1.7	0.668
PTH (pg/mL)	320 ± 281	390 ± 332	0.057
T. Cholesterol (mg/dL)	165 ± 36.5	148 ± 40.9	0.873
LDL Cholesterol (mg/dL)	91.7 ± 25.7	87.7 ± 49.9	0.066
HDL Cholestherol (mg/dL)	36.7 ± 12.8	36.9 ± 11.8	0.551
Triglycerides (mg/dL)	179.7 ± 108	169.8 ± 105	0.916

Table 5. Correlations between laboratory tests and NLR and PLR in the study population

PLR	**Parameter**	**R**	**P-value**
	NLR	0.543	< 0.001
	albumin	-0.311	0.002
	CRP	0.238	0.018
	Lymphocyte count	-0.634	< 0.001
	PLT	0.603	< 0.001
	Na	-0.228	0.023
	LDL	0.354	< 0.001
NLR	PLR	0.551	< 0.001
	CRP	0.314	0.002
	albumin	-0.261	0.009
	WBC	0.638	< 0.001
	Neutrophil count	0.705	< 0.001
	Lymphocyte count	-0.476	< 0.001
	PLT	0.543	0.042
	Na	-0.280	0.005

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; CKD = chronic kidney disease; CRP = C-reactive protein; SBP = systolic blood pressure; DBP = diastolic blood pressure; WBC = white blood cell.

Table 6. Univariate and multivariate Cox proportional hazards regression analyses of factors associated with mortality

	Univariate			Multivariate		
Characteristics	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Gender (female/male)	1.295	0.643-2.610	0.470	1.765	0.810-3.849	0.153
Age (< 55/≥ 55)	0.881	0.420-1.849	0.737	0.715	0,304-1,682	0.442
BMI median (< 19,6/≥ 19,6)	1.401	0.668-2.940	0.372	2.231	0.868-5.735	0.096
Albumin median (< 3,8/≥ 3,8)	2.078	1.029-4.194	0.041	2.107	0.836-5.310	0.114
Na (< 135/≥ 135)	2.705	1.298-5.636	0.008	4.394	1.646-11.73	0.003
Ca (< 9,5/≥ 9,5)	0.783	0.348-1.761	0.554	0.663	0.253-1.733	0.402
CRP (< 8/≥ 8)	0.507	0.246-1.045	0.066	0.561	0.239-1.322	0.186
Ferritin median (< 369/≥ 369)	1.213	0.592-2.485	0.598	1.862	0.793- 4.373	0.154
NLR median (<3,2/≥ 3,2)	0.516	0.248-1.073	0.077	0.900	0.374-2.164	0.814
PLR median (< 137,2/≥ 137,2)	0.315	0.145-0.686	0.004	0.338	0.128-0.894	0.029
Vascular acsess (AVF/PC)	0.615	0.275-1.378	0.238	0.768	0.281-2.103	0.608
PTH (< 150/≥ 150)	1.240	0.555-2.769	0.600	0.443	0.128-1.530	0.198

BMI = Body mass index; CRP = C-reactive protein; NLR = Neutrophil to lymphocyte ratio; PLR = Platelet to lymphocyte ratio, AVF: arteriovenous fistula, PC: permanent catheter.*All parameters were analysed as multivariate and univarate for mortalitiy (cox regesion analysis)

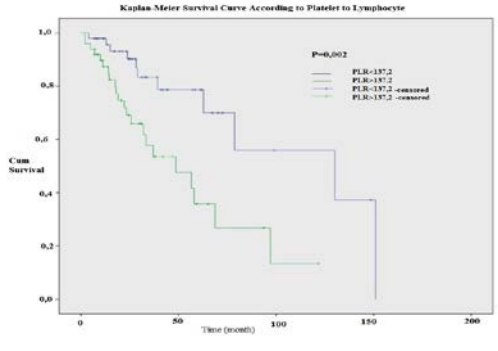

Figure 3. Kaplan–Meier survival curve according to platelet to lymphocyte ratio2

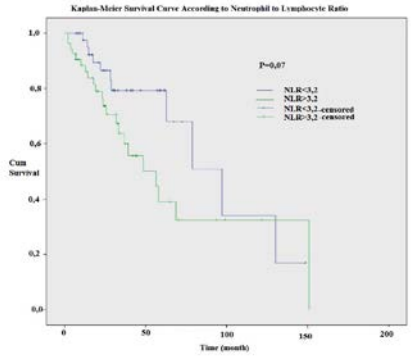

Figure 4. Kaplan-Meier survival curve according to neutrophil to lymphocyte ratio.

DISCUSSION

The most frequent causes of death in our study were cardiovascular diseases (57.6%) and other causes were infections (12.1%), malignancy (12.1%), cerebrovascular diseases (12.1%) and others (6.1%). This finding was consistent with the literature that cardiovascular diseases were the most common cause of death in dialysis patients[1,20,21]. This increased risk can not only explain traditional cardiovascular risk factors such as advanced age, female sex, smoking, HT, hyperlipidemia, and diabetes[22]. In addition to these factors in patients with CKD, inflammation, hypervolemia, malnutrition, anemia, secondary

hyperparathyroidism and bone mineral disorders are other important risk factors[23].

Inflammation is a response of vascular structures or tissues to various stimuli such as infection, trauma, toxic damage[24]. Acute and chronic pro-inflammatory conditions are common in patients with CKD and contribute significantly to increased mortality and morbidity in patients[5,24,25]. In addition, it has an important role in the progression of the disease in patients with CKD. Inflammation plays an active role in the formation of endothelial dysfunction and vascular calcification, leading to increased cardiovascular complications in these patients[25].

In patients with HD, inflammation is multifactorial and vascular access play role development of inflammation. In HD patients, catheter-related infections, thrombosed fistulas, and grafts play role development of inflammation additionally to factors known in CKD such as oxidative stress, metabolic acidosis, uremic toxins, and malnutrition. Besides, various comorbidities such as heart failure, DM, HT, chronic glomerulonephritis, and obesity, which are common in these patients, contribute to inflammation[4,25,26]. Inflammation in patients with ESRD is related to CVD including endothelial dysfunction, vascular calcification, and AS, protein-energy wasting, malnutrition, increased morbidity, and mortality[4,26-28]. It is expected that both the primary disease itself and HD treatment and vascular access, as well as persistent inflammation caused by comorbid conditions, increase mortality in HD patients.

In our study baseline PLR was found to be predictive of mortality in our HD patients. But the relationship between NLR and mortality in HD patients was not statistically significant. According to our study results, PLR and NLR correlated positively with each other and with CRP. Although both PLR and NLR correlate positively with CRP, a good indicator of systemic inflammatory response, only PLR was predictive of mortality in HD patients. This may suggest that PLR is a more sensitive indicator of systemic inflammatory response.

PLR and NLR negatively correlated with serum sodium levels in our study. In the group with median NLR $\geq$ 3.2, the serum sodium level was lower than the group with NLR < 3.2. There was no statistically significant difference between median PLR and serum sodium. The serum sodium level was found to be lower in the patients who died than in patients who were still undergoing dialysis. In multivariate analysis, serum sodium was detected as predictive for mortality as well as PLR. This may be due to the fact that the patients were more hypervolemic. Hypervolemia was found to be associated with increased mortality in hemodilysis patients[29]. In addition, hypervolemia may trigger inflammation in patients with CKD and heart failure[30-32]. Similarly increased PLR and lower serum sodium associated with mortality due to these reasons in our study.

We found that PLR and NLR correlated with negatively serum albumin and sodium, and positively with serum CRP levels. Patients with higher PLR had lower serum albumin level and higher serum CRP level. So that PLR can be more sensitive marker of inflammation, It is known that low level of serum albumin is a strong predictor of mortality in HD patients[33,34]. There was no statistically significant difference between the serum albumin and CRP levels those patients who died and surviving patients.

In our study, patients with high median PLR were found to have higher serum calcium levels than patients with lower levels. Although not statistically significant, serum PTH levels were lower in patients with high median PLR values. This may have been caused by vitamin D or other drugs, or adynamic bone disease.

In a cross-sectional study of 61 patients undergoing HD or peritoneal dialysis (PD), Turkmen at al[35]. found higher NLR, CRP, IL-6, and tumor necrosis factor alpha (TNF-α) levels as inflammatory biomarkers in PD patients than in HD patients; it has been reported that NLR is only statistically correlated with TNF-alpha. There was also no statistically significant difference between the absolute neutrophil and lymphocyte counts between HD and PD patients. The authors believe that NLR may be a predictor of inflammation in ESRD patients. In another cross-sectional study of 62 ESRD patients, it was reported that NLR, IL-6, and TNF-alpha levels were higher in patients with PLR $\geq$ 140 than patients with PLR < 139 and authors concluded that PLR was superior to NLR in terms of inflammation[36]. In another study of Ahpab at al[37]. in cross-sectional 100 HD patients, NLR and PLR were found to be positively correlated with high sensitive CRP.

Our study also supports the study in which PLR is reflecting the inflammation in dialysis patients better than NLR such as earlier study[36]. The significance detection of PLR as a predictor of mortality in our

patients and the fact that NLR does not reach this significance level suggest that PLR is a more sensitive indicator of inflammation.

In a prospective 24-month follow-up study of 80 HD patients by Yaprak at al[38]. it is determined that PLR is a predictor of 2-year mortality when it is evaluated according to NLR and PLR, and NLR does not have any association with mortality. Our study also supports the conclusion that PLR, which is reported by Yaprak at al, is a predictor of mortality in HD patients and that NLR does not show any relation. When our study is compared to Yaprak at al., ours is a retrospective study, which is a disadvantage, but it is notable that the follow-up period is longer and the number of patients is higher.

Inflammation is a major cause of mortality in HD patients. Therefore, chronic inflammation should be prevented in HD patients. Some measures should be taken to prevent inflammation; such as effort for preservation of any residual renal function, better Kt/V, more efforts for an AVF, biocompatible membranes, better quality of dialysis solution, replenishment of 25 (OH) Vit D if serum levels are low, not overzealous iron administration, nutritional support and certainly rapid confrontation of co-morbidities that may induce inflammation, such as chronic heart failure and diabetic foot[39, 40].

Our study has some limitations. These are being retrospective, single-centered, and a small number of patients. In addition, blood samples were obtained based on a single test result, so parameters such as NLR, PLR were evaluated on a single hemogram result. A latent infection or inflammation can lead to a miscalculation of the results.

In conclusion, the factors associated with mortality in our HD patients were baseline PLR and serum sodium. Interestingly, there was no correlation between mortality and age, gender, body mass index, CRP, albumin, ferritin, vascular access. As a result, PLR which is an easily accessible, inexpensive, can be a predictive biomarker for mortality in hemodialysis patients at follow up period patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BK; Veri toplama: BK; Veri analizi ve yorumlama: SP, EK, BK; Yazı taslağı: SP, EK, BK; İçeriğin eleştirel incelenmesi: SP; Son onay ve sorumluluk: BK, SP, EK; Teknik ve malzeme desteği: BK; Süpervizyon: BK; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
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