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Research Article

The Effect of Neutrophil/High-Density Lipoprotein Cholesterol Ratio on Survival in Patients on Maintenance Hemodialysis

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Abstract

Objectives: In this study, we aimed to investigate the effect of neutrophil/high-density lipoprotein cholesterol (HDL-C) ratio on survival in patients receiving maintenance hemodialysis treatment.

Methods: The files of all patients who received maintenance hemodialysis treatment as renal replacement therapy in our hospital for more than 3 months between January 1, 2016, and January 1, 2022, were retrospectively scanned (n=241). The neutrophil/ HDL-C ratio was calculated by dividing the final absolute neutrophil count by HDL-C.

Results: The study was conducted with 207 maintenance hemodialysis patients. The median age of the study group was 60 years (Q1-Q3=52–66 years). The median dialysis duration of patients was 37 months (Q1-Q3=17–45 months). It was determined that 22.7% (n=47) of the patients died during their follow-up. The median neutrophil/ HDL-C ratio was significantly higher in deceased patients than in survivors (197 vs. 123.5, p<0.001). The neutrophil/ HDL-C ratio value that best discriminated between deceased and surviving patients was found to be 146.1 with 95.7% sensitivity and 67.5% specificity (AUC=0.855, 95% CI=0.804–0.906, p<0.001). Kaplan–Meier curves revealed that the all-cause mortality rate was significantly higher in the high neutrophil/ HDL-C ratio group than in the low neutrophil/ HDL-C ratio group (log-rank p<0.001).

Conclusion: It was found that mortality was significantly increased in maintenance hemodialysis patients with a higher neutrophil/HDL-C ratio. In addition, the neutrophil/HDL-C ratio appears to be an independent risk factor for mortality in maintenance hemodialysis patients.

Keywords: Dialysis, high-density lipoprotein, mortality, neutrophils

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Peritoneal dialysis, hemodialysis, and transplantation constitute renal replacement treatment (RRT) options in a patient with end-stage renal disease. According to the Turkish Society of Nephrology registry report, hemodialysis was the most common type of RRT with 74.8% of patients who started RRT in 2019.[1] Hemodialysis patients are at increased risk of mortality for a variety of reasons. In an article published in 2019, Naylor et al.[2] showed that at unadjusted 5-year mortality, dialysis had a higher mortality from colorectal cancers in both genders, prostate cancer in men, and breast cancer in women. Many factors such as the patient's age, comorbidities, dialysis adequacy, underlying kidney disease, residual kidney function, and type of vascular access can affect overall patient survival.[3–8] Fur-

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thermore, ongoing systemic inflammation has been associated with poor outcomes in maintenance hemodialysis patients.[9, 10]

The neutrophil/high-density lipoprotein cholesterol (HDL-C) ratio (NHR) is an indicator that can be calculated using a parameter from inflammation and one from lipid metabolism.[11] While neutrophils contribute to inflammation, HDL-C plays a role as a protective factor in atherosclerotic processes. Neutrophils are the principal cells of chronic inflammation, and their high numbers increase NHR.[12] Low HDL-C is accepted as an indicator of systemic inflammation, and this low level increases NHR, too.[13] A recent study determined that there was an increase in all-cause mortality and cardiovascular events in peritoneal dialysis patients with a higher NHR.[14] We could not find any article investigating NHR on survival in hemodialysis patients.

In this study, we aimed to investigate the effect of NHR on survival in patients receiving maintenance hemodialysis treatment.

Methods

Patients and Survival

The files of all patients who received maintenance hemodialysis treatment as RRT in our hospital for more than 3 months between January 1, 2016, and January 1, 2022, were retrospectively scanned (n=241). Those who received hemodialysis treatment for <3 months (n=4), were hospitalized during routine blood tests (n=6), had an active infection (n=3), were using corticosteroids for any cause (n=5), and were diagnosed with active hematologic or oncologic cancer were excluded from the study (n=16). For survival analysis, the date of starting dialysis was subtracted from the last control date of the surviving patients and the date of death of the patients who died and expressed as months. In patients whose hemodialysis treatment was terminated due to kidney transplantation or transition to peritoneal dialysis, the date of transition to the new RRT modality was taken as the last control date. Demographic and clinical characteristics of the patients, laboratory parameters, and data about death were provided from the patient files and hospital automation system. If the patient's self-reported urine output was above 250 mL/day, residual renal function was considered to be present. While determining dialysis adequacy, the Kt/V average in the first 3 months of dialysis was evaluated. In line with KDOQI recommendations, patients with Kt/V ≥1.4 were recorded as dialysis adequacy, and patients with Kt/V<1.4 were recorded as patients without dialysis adequacy.[15]

NHR

For the neutrophil count, absolute neutrophil counts, one of the parameters of the complete blood count, which were measured for 3 consecutive months from the time, the patients started hemodialysis, were recorded and the arithmetic mean of these three measurements was taken as the final absolute neutrophil count. HDL-C value was obtained from laboratory tests performed just before the start of hemodialysis. NHR was calculated by dividing the final absolute neutrophil count by HDL-C. All laboratory tests were analyzed in the central laboratory of our hospital with an automated integrated analyzer (Cobas 6000, Roche, Switzerland).

Statistical Analysis

Categorical variables were presented as percentage and frequency. The Shapiro–Wilk test was used for the conformity of continuous variables to normal distribution. The mean and standard deviation were used to present normally distributed continuous variables, while the median and interquartile range of 1 and 3 (Q1-Q3) were used to present non-normally distributed continuous variables. The Chi-square test was used to compare categorical variables between deceased and surviving patients. Continuous variables were compared with the independent samples t-test in cases with normal distribution between the groups, and with the Mann–Whitney U-test when there was no normal distribution. ROC curves were used to determine NHR values that could predict mortality. The Youden index was used to determine the best NHR value that could be used as a mortality predictor. Patients were regrouped according to the best NHR cutoff value determined. Kaplan–Meier survival analysis and log-rank test were used to determine whether the NHR value would be a risk factor for mortality. Univariate and multivariate Cox regression analysis was performed to identify potential and independent risk factors for mortality. Statistical analyzes were done with SPSS 26.0 (IBM Corp. 2019 IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.) package program. Values with p<0.05 were expressed as statistically significant.

Results

Our study included 207 maintenance hemodialysis patients. The median age of the study group was 60 years (Q1-Q3=52–66 years). The median dialysis duration of patients was 37 months (Q1-Q3=17–45 months). It was determined that 22.7% (n=47) of the patients died. Characteristic features of the groups are presented in Table 1. The comparison of patients in terms of laboratory parameters is shown in Table 2.

The NHR value that best discriminated between deceased and surviving patients was found to be 146.1 with 95.7%

Table 1. Comparison of the groups in terms of characteristics

Characteristic	Deceased (n=47)	Survived (n=160)	Total (n=207)	p
Female gender, %-n	46.8-22	45-72	45.4-94	0.869
Median age, years	66 (62-69)	57 (49-65)	60 (52-66)	<0.001
Median dialysis duration/week, hours	12 (12-12)	12 (12-12)	12 (12-12)	0.811
Hypertension, %-n	95.7-45	85.6-137	87.9-182	0.075
Diabetes mellitus, %-n	91.5-43	52.5-84	61.4-127	<0.001
Coronary artery disease, %-n	57.4-27	29.4-47	35.7-74	0.001
Congestive heart failure, %-n	29.8-14	8.1-13	13-27	<0.001
Cerebrovascular disease, %-n	25.5-12	2.5-4	7.7-16	<0.001
Vascular Access				
Fistula, %-n	23.4-11	90-144	74.9-155	<0.001
Tunneled cuffed catheter, %-n	76.6-36	10-16	25.1-52	
Dialysis adequacy				
Kt/V≥1.4, %-n	40.4-19	88.1-141	77.3-160	<0.001
Kt/V<1.4, %-n	59.6-28	11.9-19	22.7-47	
Residual kidney function				
Present, %-n	6.4-3	36.9-59	30-62	<0.001
Absent, %-n	93.6-44	63.1-101	70-145	

Table 2. Comparison of the groups in terms of laboratory parameters

Laboratory test	Deceased (n=47)	Survived (n=160)	Total (n=207)	p
Urea, mg/dL	184 (129-215)	173 (138-206)	184 (138-206)	0.987
Creatinin, mg/dL	7.39 (7.1-9.9)	7.74 (7-8.1)	7.7 (7-8.1)	0.303
Albumin, g/dL	3 (3-3.2)	4 (3.6-4.3)	3.99 (3.2-4.2)	<0.001
Sodium, mmol/L	137 (132-138)	135 (131-138)	136 (130-138)	0.112
Potassium, mmol/L	4.4 (3.9-5)	4.7 (4.1-5.4)	4.7 (4.1-5.2)	0.170
Calcium, mg/dL	8.4 (8.1-9)	8.6 (8.1-9.1)	8.4 (8.1-9.1)	0.139
Phosphorus, mg/dL	5 (4.7-6)	5.2 (4.7-5.9)	5.2 (4.7-6)	0.137
Leukocyte, 10^3 µL	7.13 (5.9-9.9)	8.6 (5.9-9.5)	8.44 (5.9-9.5)	0.959
Neutrophil, 10^3 µL	5.1 (5-5.33)	4.63 (3.7-5.7)	5.1 (3.7-5.7)	0.025
Hemoglobin, g/dL	10.8 (10-12.5)	10.9 (9.9-12.2)	10.9 (9.9-12.2)	0.994
Platelet, 10^3 µL	186 (180-221)	215 (169-265)	199 (176-265)	0.330
Parathyroid hormone, ng/L	223 (116-451)	225 (126-316)	223.8 (126-398)	0.954
C-reactive protein, mg/dL	1 (0.6-4)	1.6 (0.63-5)	1.6 (0.6-5)	0.207
TC, mg/dL	158.3±46.9	171.5±53.4	168.5±52.2	0.129
LDL-C, mg/dL	106 (76-131)	110 (76-136)	110 (76-136)	0.538
HDL-C, mg/dL	32.5±8.3	38.4±11.1	37.1±10.8	0.001
Triglyceride, mg/dL	119 (86-183)	141 (90-189)	136 (90-183)	0.296
NHR	197 (175-233)	123.5 (94-164)	140 (108-191)	<0.001

TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

sensitivity and 67.5% specificity (AUC=0.855, 95%CI=0.804–0.906, p<0.001). Fig. 1 shows the ROC curve for NHR to differentiate between the deceased and survivors. When the patients were divided into two groups with NHR<146.1 and NHR≥146.1, it was found that 53.1% (n=10) were in the group with low NHR and 46.9% (n=97) were in the group with high NHR. Survival rates were 90.9% versus 61.9% in the low-NHR and high-NHR groups, respectively. Kaplan–Meier curves revealed that the mortality rate was higher in the high-NHR group than in the low-NHR group (log-rank p<0.001) (Fig. 2).

Table 3. Univariate and multivariate Cox regression analysis of possible risk factors for mortality

	Univariate		Multivariate	
Parameter	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, per year	1.098 (1.051-1.146)	<0.001	1.048 (0.992-1.108)	0.091
Diabetes mellitus	4.915 (2.184-11.061)	<0.001	2.440 (0.958-6.211)	0.061
Coronary artery disease	1.918 (1.074-3.426)	0.028	2.463 (1.173-5.181)	0.017
Congestive heart failure	2.656 (1.303-5.413)	0.007	1.500 (0.636-3.535)	0.354
Cerebrovascular disease	4.499 (2.215-9.138)	<0.001	1.945 (0.844-4.482)	0.118
Vascular access, (reference= fistula)				
Catheter	9.070 (4.918-16-728)	<0.001	4.115 (1.823-9.285)	0.001
Dialysis adequacy, (reference= Kt/V≥1.4)				
Kt/V<1.4	4.577 (2.569-8.156)	<0.001	1.846 (0.908-3.754)	0.090
Residual kidney function, (reference= present)				
Absent	3.888 (1.536-9.843)	0.004	1.844 (0.689-4.936)	0.223
Serum albumin, per g/dL	0.114 (0.057-0.228)	<0.001	0.386 (0.149-0.999)	0.050
NHR group, (reference <146.1)				
≥146.1	5.461 (2.712-10.996)	<0.001	2.310 (1.037-5.141)	0.040

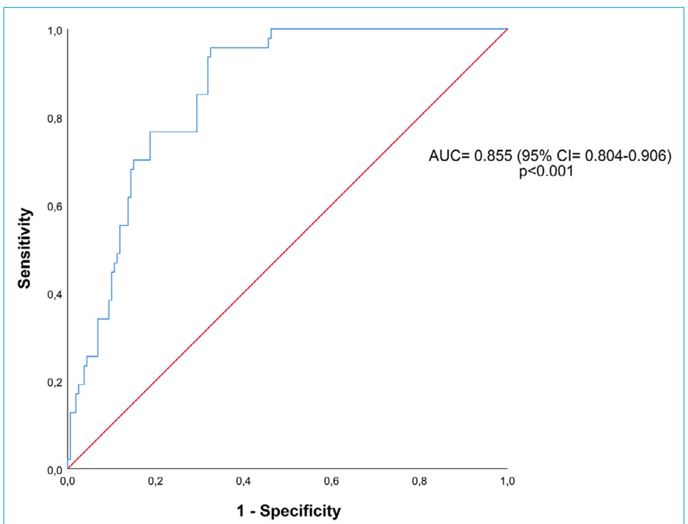

Figure 1. ROC curve for NHR to differentiate between the deceased and survivors.

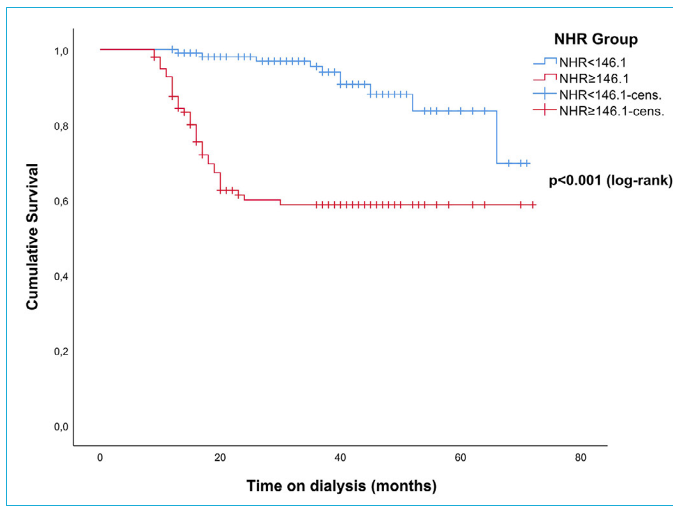

Figure 2. Survival of patients in terms of the NHR group.

To evaluate the independent risk factors for mortality, a multivariate Cox regression model was performed with the parameters found to affect mortality in the univariate Cox regression analysis. Our regression model included age, serum albumin, presence of diabetes, presence of coronary artery disease, presence of congestive heart failure, presence of cerebrovascular disease, vascular access, dialysis adequacy, residual kidney function, and NHR groups. Coronary artery disease, use of a catheter as a vascular access route, decreased serum albumin level, and being in the high-NHR group were determined as independent risk factors for mortality (p=0.017, p=0.001, p=0.050, and p=0.040, respectively).

Discussion

Our study shows that overall survival is significantly reduced in patients receiving maintenance hemodialysis therapy with increased NHR, a marker of systemic inflammation. This is the first study to investigate the effect of NHR on mortality in hemodialysis patients. In a multicenter 2-year follow-up study by do Sameiro-Faria et al.,[16] systemic inflammation was found to be a risk factor for mortality in hemodialysis patients. In their study, they evaluated systemic inflammation with high-sensitivity CRP. Although high-sensitivity CRP can be used as a standard test by many centers, it has not yet been widely used in clinical practice, especially in underdeveloped and developing countries. In this sense, there is a need for an inexpensive and easily accessible marker of inflammation. The previous studies support that NHR can be used as an indicator of systemic inflammation in various conditions.[17–19] Our study is not the first to investigate the effect of NHR on mortality in patients receiving RRT. NHR was found to be an independent risk factor for all-cause mortality in peritoneal dialysis patients in the study of Li et al.[14] Our findings support that NHR is also an independent risk factor for mortality in hemodialysis patients. It is not clear how NHR can predict mortality, but it is a known fact that systemic inflammation is high in hemodialysis patients. NHR may be a useful marker of systemic inflammation in patients on maintenance hemodialysis.

Causes of death were not investigated in our study, but cardiovascular deaths were proven to be the major cause of death in hemodialysis patients. In a recent cohort study of 3528 maintenance hemodialysis patients with 10 years of follow-up, cardiovascular events were found as the major cause of death.[20] In a multicenter cohort study involving more than 220,000 patients, in which the trend of causes of death in patients receiving maintenance hemodialysis treatment was investigated, cardiovascular causes were found as the major cause of death in hemodialysis patients, although it decreased compared to the previous years.[21] The finding of coronary artery disease as an independent risk factor for mortality in our study matches this information in the literature.

Low albumin levels are related to mortality in several diseases. de Mutsert et al.[22] found that a 1 g/dL decrease in albumin in hemodialysis patients increased the mortality risk by 47%. Albumin may decrease as a negative-acute phase reactant caused by systemic inflammation in hemodialysis patients and it is also a strong indicator of malnutrition.[23] In our study, we found that the risk of mortality significantly decreased by 61.4% for each 1 g/dL increase in albumin level in patients on maintenance hemodialysis (hazard ratio=0.386; 95% CI=0.149–0.999).

Arteriovenous fistulas are the first recommended vascular access route in patients receiving RRT with maintenance hemodialysis. The results of studies investigating the relationship between vascular access type and mortality in maintenance dialysis patients are controversial. In the literature, some studies have found that the risk of mortality is lower in those undergoing hemodialysis with an arteriovenous fistula, while in others, mortality rates were found to be similar between arteriovenous fistula and tunneled cuffed dialysis catheters.[24–27] Tunneled cuffed dialysis catheters have a risk of systemic infection compared to arteriovenous fistula.[28] In our study, we found that the use of a catheter as a vascular access route in maintenance hemodialysis patients is an independent risk factor for mortality. We think that catheters may increase the risk of mortality by causing an increase in systemic inflammation, even if the patient has no clinical signs of infection.

Limitations of our study are retrospective design, being single-center, and not including the malnutrition status. However, our study is important because it is the first study to evaluate NHR on mortality in maintenance hemodialysis patients. Multicenter and prospective studies, including patients' malnutrition status, may reveal the effects of NHR on mortality in maintenance hemodialysis patients more clearly.

Conclusion

We found that survival of maintenance hemodialysis patients decreased significantly as NHR increased. In our study, NHR was found to be an independent risk factor for mortality, together with coronary artery disease, vascular access with the catheter, and low albumin.

Disclosures

Ethics Committee Approval: The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Meeting date: November 4, 2022, Meeting number: 2022/14, Decision number: 522). Since the study was retrospective, there was no patient consent and the study was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest: None declared.

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