Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1311565
J Health Sci Med. 2023;6(5):1010-1015

Prognostic value of inflammatory markers for mortality in hemodialysis patients: a retrospective study with over 3-year follow-up

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Cite this article as: Yazıcı R, Güney İ. Prognostic value of inflammatory markers for mortality in hemodialysis patients: a retrospective study with over 3-year follow-up. *J Health Sci Med.* 2023;6(5):1010-1015.

Received: 08.06.2023 ◆ **Accepted**: 03.09.2023 ◆ **Published**: 28.09.2023

ABSTRACT

Aims: In chronic kidney disease (CKD), chronic systemic inflammation contributes to premature ageing and morbidity; it is a predictor of overall mortality. In this study, we aimed to investigate prognostic value of inflamatory markers including systemic immune-inflammation index (SII), pan-immune-inflammation value (PIV), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for mortality outcomes in hemodialysis patients.

Methods: In this retrospective study, CKD patients on maintenance hemodialysis between January 1, 2020 and January 31, 2020 were included. SII, PIV, NLR, PLR values of the patients were calculated. SII was calculated by (neutrophil count x platelet count)/lymphocyte count; PIV was calculated by (neutrophil count x platelet count x monocyte count)/lymphocyte count. Mortality rate of the study population during approximately 38-month follow-up period was calculated. The relationships of inflamatory markers and other variables with mortality were analysed.

Results: Of 162 patients, 53.1% were male and 46.9% were female (mean age: 61.6±13.5). During 38-month follow-up period, a total of 60 patients (37%) died. Compared with surviving group, NLR values, mean age and the rate of diabetes mellitus (DM) and coronary artery disease (CAD) comorbidities were higher (p=0.012, p <0.001, p=0.008, p <0.001 respectively) and albumin, uric acid and creatinin levels were lower (p <0.001, for each) in the nonsurvivor group. There was no difference between these two groups in terms of PIV and SII values and CRP levels. In Cox regression analysis, presence of CAD (Exp ß: 2.116; 95% CI, 1.222-3.648; p=0.007), age (Exp ß: 1.049; 95% CI, 1.022-1.077; p <0.001), serum uric acid (Exp ß: 0.721; 95% CI, 0.559-0.929; p=0.011) and albumin levels (Exp ß: 0.395;95% CI, 0.158-0.984, p=0.046), NLR (Exp ß: 1.345; 95% CI, 1.152-1.1570; p <0.001) and PLR (Exp ß: 0.993; 95% CI, 0.989-0.997; p=0.002) were found to be associated with mortality.

Conclusion: There was no difference between nonsurviving and surviving group in terms of PIV and SII values and CRP levels. Age, presence of CAD, serum uric acid and albumin levels and NLR and PLR values were associated with all-cause mortality, independently. Prospective studies with larger number of hemodialysis patients and serial measurements of inflammatory markers are needed.

Keywords: Hemodialysis, systemic immune-inflammation index, pan-immune-inflammation value, mortality, inflammatory markers

INTRODUCTION

During the course of chronic kidney disease (CKD) progression, there is a gradual decrease in kidney function, which may eventually lead to the necessity of renal replacement therapy (RRT). Hemodialysis is one of the most important RRT and despite the developments in hemodialysis technology, the mortality rate among hemodialysis patients is still high.[1,2] Some factors such as age, albumin levels, comorbid conditions, underlying kidney disease, cardiovascular and psychosocial status, residual renal function, dietary factors, etc, may affect mortality rates in hemodialysis patients.[2,3]

In CKD patients, chronic systemic inflammation has multifactorial etiology; it contributes to premature ageing and morbidity (especially cardiovascular disease, malnutrition and anemia) and it is a predictor of all-cause mortality.[4] In some previous studies in hemodialysis patients, it was reported that the increased systemic inflammation-based prognostic scores including Glasgow prognostic score and modified Glasgow prognostic score (inflammation-based scores based combination of albumin and CRP levels), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte

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ratio (PLR), prognostic index and prognostic nutritional index were associated with mortality during 42-month follow-up; and inflammation scores, which include NLR, monocyte-to-lymphocyte ratio and PLR, might be useful in predicting prognosis and all-cause mortality.[5,6]

The systemic immune-inflammation index (SII), calculated using neutrophil, platelet and lymphocyte counts has recently been introduced as a new and powerful prognostic marker in cancer patients.[7,8] In a study conducted in Turkey, it has been showed that high SII could predict mortality in cancer patients receiving palliative care.[9] In a recent study, it was reported that pan-immune-inflammation value (PIV) (a novel inflamatory marker calculated using neutrophil, platelet, monocyte and lymphocyte counts) was significantly associated with an increased risk of all-cause mortality in peritoneal dialysis patients.[10] In the literature, there is limited data about relation between SII and mortality outcomes of hemodialysis patients.[11,12] As far as we know, there is no data about prognostic value of PIV in hemodialysis patients.

In this retrospective study, we aimed to investigate prognostic value of inflamatory markers including SII, PIV, NLR and PLR for mortality outcomes and also to investigate other factors related with all-cause mortality in hemodialysis patients during 38-month follow-up period.

METHODS

The study was carried out with the permission of by KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/018). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, CKD patients (aged >18 years) who were continuing on maintenance hemodialysis in dialysis center between January 1, 2020 and January 31, 2020 were included. The patients on hemodialysis less than 3 months; the patients who had acute or chronic infection, who had rheumatological or hematological disease; the patients under immunesuppressive or anti-inflammatory treatment and the patients with missing data were excluded from the study.

Demographical, clinic and laboratory data of patients, such as age and gender, primary cause of kidney disease, comorbid conditions, smoking status, hemoglobin level, neutrophil, lymphocyte, platelet count, Kt/V value, serum lipids, creatinine, sodium, potassium, parathormon, ferritin, phosphorus, calcium, uric acid, C-reactive protein (CRP) and albumin levels were obtained from the patients' file records. Blood samples for routine blood tests were taken before dialysis. In all patients in this study, hemodialysis was performed with heparin except two patients with high risk of bleeding. NLR, PLR, SII and PIV of the patients were calculated. SII was calculated by (neutrophil count x platelet count)/lymphocyte count; PIV was calculated by (neutrophil count x platelet count x monocyte count)/lymphocyte count. NLR ratios were also grouped as 'low' and 'high' with cut-off value of 3 (<3 and ≥3 respectively).[13]

For mortality outcomes, the patients' clinical status on April 1, 2023 were detected from the medical records and the mortality rate of the study population during this approximately 38- month follow-up period was calculated. The relationships of the inflamatory markers (SII, PIV, NLR and PLR) and also other variables with mortality were analysed.

Statistical Analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) for Windows version 22 program. Categorical variables were compared using Chi-square test. T-test and Mann Whitney U test were used for comparisons between groups. Backward Cox regression analysis was used to identify independent variables related with mortality. In Cox-regression analysis, parameters with $p < 0.1$ in paired comparison tests (T-test, Mann Whitney U test and Chi-square test) were included (age, CAD, DM, NLR, PLR, SII, serum creatinine, uric acid, albumin, phosphorus, lymphocyte, vascular access). P values <0.05 were accepted as statistically significant.

RESULTS

A total of 195 patients were included in the study at the beginning. But, during follow-up period, 27 patients were transferred to other hemodialysis centers, 3 patients underwent renal transplantation and hemodialysis was discontinued in two patients. Finally, data of remaining 162 patients were analysed. Mean age was 61.6±13.5; 76 patients (46.9%) were female and 86 (53.1%) were male. Median time on hemodialysis was 65.5 (3-324) months. Underlying etiologies for kidney failure were diabetes mellitus (DM) (52 patients, 32.1%), hypertension (37 patients, 22.8%), polycystic kidney disease (15 patients, 9.3%), urological causes (15 patients, 9.3%), glomerulonephritis (12 patients, 7.4%), other etiologies (12 patients, 7.4%) and unknown underlying etiologies (15 patients, 9.3%). As vascular access for hemodialyis, 123 patients (76.9%) had arteriovenous fistula (AVF) or arteriovenous graft (AVG); 39 patients (24.1%) had central venous catheter (CVC). Of the patients, 107 (66%) had hypertension; 69 (42.6%) had coronary artery disease (CAD); 66 (40.7%) had DM; 19 (11.7%) had chronic obstructive pulmonary disease as comorbid diseases; 39 patients (24.1%) had smoking history. Median PIV and

SII values of all study group were 431 (5-3570) and 835.5 (112.5-7843.7) respectively. Demografic, clinical and laboratory features of the study population were shown in Table 1. During 38-month follow-up period, a total of 60 patients (37%) died; remaining 102 patients (63%) were on hemodialysis.

When the group of patients who died and those surviving were compared, NLR values (as absolute value and as grouped with specific cut-off value of 3, p=0.012 and p=0.035 respectively), mean age (p <0.001) and the rate of DM (p=0.008) and CAD comorbidities (p <0.001) were higher and serum albumin, uric acid and creatinin levels were lower (p <0.001, for each) in the group of patients who died (Table 1). As vascular access for hemodialyis, 66.7% of patients had AVF/AVG and 33.3% had CVC in nonsurviving group; these numbers in surviving group were 82.2% and 17.8%, respectively (p=0.034) (Table 1). There was no differences between these two groups in terms of PIV, SII values, CRP, ferritin, serum lipids and the other parameters (Table 1).

Table 1. Baseline characteristics of the patients and comparison of survivor and nonsurvivor groups

Parameter	All patients(n=162)	Survivors(n=102)	Nonsurvivors(n=60)	P value
Age, year	61.6±13.5	57.513.5	68.7±10.5	<0.001
Gender,				0.961
Female, n(%)	76 (46.9%)	48 (47.1%)	28 (46.7%)	
Male, n(%)	86 (53.1%)	54 (52.9%)	32 (53.3%)	
Smoker, n(%)	39 (24.1%)	24 (23.5%)	15 (25%)	0.234
Presence of diabetes, n (%)	66 (59.3%)	33 (32.7%)	33 (55.0%)	0.008
Presence of hypertension, n (%)	107 (66.0%)	63 (62.4%)	44 (73.3%)	0.174
Presence of COPD, n (%)	19 (11.7%)	11 (10.9%)	8 (13.3%)	0.625
Presence of CAD, n (%)	68 (42.0%)	32 (30.7%)	37 (61.7%)	<0.001
Vascular access,				0.034
AVF/AVG	123 (76.0%)	83 (82.2%)	40 (66.7%)	
CVC, n(%)	39 (24.0%)	19 (17.8%)	20 (33.3%)	
Hemodialyis vintage, month	65.5 (3-324)	45.5 (3-226)	49.0 (3-324)	0.504
PIV value	431.1 (5-3570)	280.9 (5.6-3570.7)	322.3 (22.3-3423.9)	0.162
SII value	835.3 (112.5-7843.8)	607.8 (112.5-7540.8)	711.5 (139.4-7843.5)	0.062
NLR value	3.62 (0.9-43.8)	2.79 (0.90-18.1)	3.21 (1.2-43.8)	0.012
< 3	83 (51.2%)	59 (% 57.8)	24 (% 40)	0.035
≥ 3	77 (48.8%)	43 (% 42.2)	36 (% 60)	0.035
PLR value	168 (51-1737)	134.7 (53.9-1737.5)	155.9 (51.5-1627.3)	0.087
Hemoglobin, g/dl	12.7±1.6	12.8±1.6	12.7±1.6	0.649
Monocyte, 10^3/µl	0.50±0.25	0.51±0.26	0.50±0.23	0.853
RDW, %	14.1 (9.6-20.4)	14.0 (9.9-19.3)	13.8 (9.6-20.4)	0.931
MPV, µm^3	8.16 (5.6-14.8)	7.9 (5.9-13.5)	8.1 (5.6-14.8)	0.312
Neutrophil, 10^3/µl	4.9 (0.72-11.8)	4.5 (0.72-10.90)	4.79 (1.68-11.80)	0.459
Lymphocyte, 10^3/µl	1.69 (0.11-4.54)	1.68 (0.24-4.54)	1.47 (0.11-3.67)	0.075
Platelet, 10^3/µl	228.7 (74.5-454.0)	227.5 (91.1-454.0)	215 (74.5-443.0)	0.548
Serum albumin, g/dl	3.9 (2.1-4.8)	4.0 (2.6-4.8)	3.8 (2.1-4.5)	<0.001
Serum uric acid, mg/dl	5.7±1.0	6.0±1.0	5.4±1.0	<0.001
C-reactive protein, mg/L	12.2 (0.1-144)	138 (132-144)	138 (129-143)	0.784
Serum creatinine, mg/dl	7.8±2.1	8.4±2.2	7.0±1.7	<0.001
Calcium, mg/dl	8.7±0.8	8.6±0.8	8.8±0.7	0.107
Potassium, mmol/L	4.9±0.65	4.96±0.64	4.81±0.67	0.140
Phosophorus, mg/dl	4.8 (1.7-9.9)	5.0 (1.7-8.5)	4.6 (2.2-9.9)	0.079
Sodium, mmol/L	138.7 (129-143)	138 (132-144)	138 (129-143)	0.784
Triglyserides, mg/dl	189.0 (42.0-822.0)	164.0 (42.0-603.0)	162.5 (48.0-822)	0.820
HDL-cholesterol, mg/dl	37.5 (15.0-78.0)	37.0 (15.0-78.0)	36.0 (20.0-64.0)	0.628
LDL-cholesterol, mg/dl	89.7 (40.0-210.0)	85.0 (40.0-210.0)	87.5 (40.0-183.0)	0.864
Triglyserides/ HDL-cholesterol	5.87 (1.04-39.14)	4.75 (1.04-23.19)	4.6 (1.17-39.14)	0.880
ALT, U/L	15.3 (1.0-100.0)	12.0 (1.0-100.0)	12.0 (1.0-66.0)	0.824
Ferritin, µg/L	805.2 (11.9-1650)	603.2 (47.9-1650)	855.0 (11.9-1650)	0.213
Parathormon, ng/L	562.5 (0.1-2941)	495.4 (0.1-2941.9)	422.6 (12.5-1862.5)	0.600
HbA1c, %	7.0 (4.1-13.2)	6.6 (4.1-13.2)	6.9 (5.4-11.1)	0.247
Kt/V	1.6 (0.95-2.19)	1.6 (0.95-2.19)	1.61 (1.36-1.97)	0.295

Data are given as mean±SD or median (minimum-maximum). Abbreviations: COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; AVF/AVG, arteriovenous fistula/arteriovenous graft; CVC, central venous catheter; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution width; MPV, mean platelet volume; HDL, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; HbA1c, glycosylated hemoglobin.

In Backward Cox regression analysis, performed to determine the independent markers of mortality, the parameters with p <0.1 in paired comparison tests (age, CAD, DM, NLR, PLR, SII, uric acid, albumin, phosphorus, lymphocyte, serum creatinine, vascular access) were included and presence of CAD (Exp ß: 2.116; 95% CI, 1.222-3.648; p=0.007), age (Exp ß: 1.049; 95% CI, 1.022-1.077; p <0.001), serum uric acid (Exp ß: 0.721; 95% CI, 0.559-0.929; p=0.011) and albumin levels (Exp ß: 0.395;95% CI, 0.158-0.984, p=0.046), NLR (Exp ß: 1.345; 95% CI, 1.152-1.1570; p <0.001) and PLR (Exp ß: 0.993; 95% CI, 0.989-0.997; p=0.002) were found to be associated with mortality, independently (Table 2).

Table 2. Cox regression analysis (Backward) to determine independent variables

Variable	Model 1 Chi-square=66.008 P Exp(B) CI %95	Model 6 Chi-square=65.231 P Exp(B) CI%95
Presence of CAD	0.005 2.317 (1.284-4.182)	0.007 2.116 (1.228-3.648)
Age, year	0.001 1.047 (1.018-1.076)	<0.001 1.049 (1.022-1.077)
NLR value	0.004 1.328 (1.093-1.613)	< 0.001 1.345 (1.152-1.570)
PLR value	0.001 0.993 (0.988-0.997)	0.002 0.993 (0.989-0.997)
Lymphocyte, 10^3/µl	0.996 0.999 (0.636-1.569)	0.084 1.907 (0.916-3.969)
Serum uricacid, mg/dl	0.007 0.674 (0.505-0.899)	0.011 0.721 (0.559-0.929)
Serum albumin, g/dl	0.034 0.329 (0.118-0.918)	0.046 0.395 (0.158-0.984)
Presence of diabetes	0.886 0.958 (0.535-1.716)	
SII value	0.753 1.000 (0.999-1.001)	
Phosophorus, mg/dl	0.503 1.103 (0.828-1.469)	
Serum creatinine, mg/dl	0.748 1.029 (0.863-1.227)	
Vascular access	0.251 0.721 (0.413-1.260)	

Parameters with p <0.1 in paired comparison tests were included in the Cox regression analysis. Abbreviations: CAD, coronary artery disease; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

DISCUSSION

Findings of this study showed that all-cause mortality rate in our hemodialysis patients was 37% during 38-month-follow-up period and age, presence of CAD, serum uric acid and albumin levels and NLR and PLR values were associated with all-cause mortality.

In a previous study from Turkey, mortality rate in hemodialysis patients was reported to be 39.2% during 4-year follow-up.[2] In United States Renal Data System, the mortality rate in 2016 was 166 per 1,000 patient-years for hemodialysis patients.[1] In a study from Japan, all-cause mortality rate among hemodialysis patients was 29.1% during 42-month follow-up.[5]

In our study, in the group of patients who died during follow-up period, NLR values, age and the rate of DM and CAD as comorbidities were higher; whereas albumin, uric acid and creatinin levels were lower; there was no differences between nonsurviving and surviving group in terms of PIV and SII values and CRP levels. A recent study including a part of the MONitoring Dialysis Outcomes (MONDO) participants, nonsurviving patients were older, and they had lower albumin and creatinin levels, and higher levels of inflammatory markers (white blood cell count, neutrophil count, NLR, CRP) at baseline.[14] Findings of this study showed that these inflammatory markers which decreased after initiation of hemodialysis, increased approximately 6 months preceding death; whereas lymphocyte count, serum albumin, and hemoglobin levels, which increased after hemodialysis initiation, decreased in months before death.[14]

In a retrospective study, higher inflammation scoring including monocyte-to-lymphocyte ratio, NLR and PLR was found to be independently associated with all-cause mortality in hemodialysis patients, whereas CRP, a traditional marker of inflammation, was not associated with mortality.[6] Unlike our study, in one of limited number of the previous studies investigating the relationship between SII and prognostic outcomes in hemodialysis patients, 1-year cumulative survival rate was reported to be lower in SII high group.[12] These may be atributed to the different follow-up times, different sample size and methodology between studies. In a study in coronavirus disease-2019 (COVID-19) hemodialysis patients, it was concluded that SII could be used to predict the need for intensive care unit and mortality risk.[11] However, in another study in maintenance hemodialysis patients with COVID-19, SII was not found as an independent risk factor for mortality in the multivariate regression analysis; it was reported that NLR had favorable predictive value and SII did not contribute more than NLR in predicting mortality.[15] In the study of Kato et al.[5], it was shown that increased Glasgow prognostic score/modified Glasgow prognostic score (inflammation-based scores including combination of albumin and CRP levels), NLR and PLR values were associated with all-cause mortality in hemodialysis patients. Our Cox regression analysis revealed that, age, presence of CAD, serum uric acid and albumin levels and NLR and PLR values were associated with all-cause mortality, independently. Similarly, in the study of Alanlı et al.[2], older age, low albumin levels and low left ventricle ejection fraction values were among the factors related with increased mortality risk in hemodialysis patients. Albumin level is related with inflamation and nutritional status. Inflamation and malnutrition which are prevalent in hemodialysis patients, are interrelated creating a vicious cycle and closely linked to atherosclerosis-

related cardiovascular diseases: They all contribute to the increased risk of morbidity and mortality in hemodialysis patients.[16] Regarding uric acid level, our nonsurviving group had lower uric acid level and our Cox regression analysis showed that uric acid level associated with all-cause mortality, in accordance with the studies of Li et al.[16] and Murea et al.[17] Underlying mechanism of this effect in hemodialysis patients is speculative.[18] In the study of Li et al.[16] uric acid levels were found to be correlated with nutritional and inflammatory status.

We could not found any data about prognostic value of PIV in hemodialysis patients. Unlike our study, in a previous study in peritoneal dialysis patients, PIV value was significantly associated with an increased risk of all-cause mortality.[10] In the study of Kazan et al.[18] it was reported that PIV and SII values might be useful in predicting remission in low-moderate risk idiopathic membranous nephropathy patients.

There are some limitations of our study: First, it is a single center and retrospective study with relatively small sample size and it would be better to perform aditional analysis in subgroups that match each other regarding parameters that affect mortality such as age, CAD, etc. Second, according to our study design, we performed analyzes on a single measurement in patients undergoing dialysis within a specified time period. It might be more appropriate to investigate the prognostic value of inflammation markers, including SII, PIV, NLR and PLR, for mortality by performing 6-month serial measurements starting from the initiation of hemodialysis and even just before hemodialysis. These may be considered in future studies.

CONCLUSION

Our findings showed that, there was no difference between the nonsurviving group and the surviving group in terms of PIV and SII values and CRP levels. In the group of patients who died during follow-up period, NLR values were higher; age, presence of CAD, serum uric acid and albumin levels and NLR and PLR values were associated with all-cause mortality, independently. To determine prognostic role of inflammatory markers for mortality in hemodialysis patients, prospective studies with larger number of patients and serial measurements of inflammatory markers are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of by KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/018).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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