Disease and Diagnosis

Dis Diagn. 2024; 13(2):80-84

doi 10.34172/ddj.1567

Original Article

The Relationship of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio with High Sensitivity C-Reactive Protein Level in Hemodialysis Patients

Marzieh Kazerani[1*], Sara Raji[2], Fatemeh Javadi Rad[1], Mahdi Mottaghi[2]

[1]Department of Infectious Disease, Mashhad Islamic Azad University of Medical Sciences, Mashhad, Iran
[2]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran

***Correspondence to**
Marzieh Kazerani
Email: Kazerani1617@mshdiau.ac.ir, mkazerani@yahoo.com

Abstract

Background: Hemodialysis (HD) is the treatment of end-stage renal disease (ESRD), which leads to increased inflammation and mortality. This study aimed to investigate the relationship of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with high sensitivity C-reactive protein (hs-CRP) levels to predict inflammatory conditions in HD patients.

Materials and Methods: A total of 100 eligible maintenance HD patients referred to 22 Bahman and 17 Shahrivar hospitals in Mashhad were enrolled in this cross-sectional study. We collected demographic and clinical data, as well as values of inflammatory markers such as NLR, PLR, and hs-CRP, from the patient's medical records.

Results: Forty-six of the patients were female. The mean age of the patients was 37.96 ± 10.29 years, and the mean duration of HD was 54.32 ± 50 months. The mean hs-CRP levels, NLR, and PLR were 6.08 ± 5.70 mg/L, 2.79 ± 1.18, and 125.80 ± 57.14, respectively. The results showed a statistically significant and direct relationship between PLR and hs-CRP levels (P=0.01). There was no correlation between NLR and hs-CRP levels (P=0.8). Additionally, PLR was inversely correlated with hs-CRP in hypertensive patients (r=-0.283, P=0.04), female patients (r=0.3, P=0.04), and patients with HD duration of less than five years (r=0.3, P=0.001).

Conclusion: Based on these findings, the PLR is a useful inflammatory marker in HD patients with ESRD that correlates with hs-CRP levels. We recommend further investigations to establish its accuracy in clinical care.

Keywords: Chronic kidney disease, C-reactive protein, Renal dialysis, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio

Received: October 21, 2023, **Accepted:** December 12, 2023, **ePublished:** February 26, 2024

Introduction

The definition of chronic kidney disease (CKD) is based on the estimated glomerular filtration rate of less than 60 mL/min/1.73m^2 for at least three months (1,2). CKD is a major cause of morbidity and mortality worldwide (1). In CKD, cardiovascular complications are among the leading causes of mortality, and these complications are mediated by systemic inflammation (3,4). Various biomarkers, such as total lymphocyte count, C-reactive protein (CRP), interleukin (IL)-6, IL-18, tumor necrosis factor-alpha (TNF-α), and pentraxin-3 have been suggested to evaluate systemic inflammation (5,6). Patients with hemodialysis (HD) are particularly prone to inflammation-related atherosclerotic vascular disease, which leads to higher rates of hospitalization and mortality (3,7). In recent years, novel biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) with a standard range of 1.7 ± 0.7 (8), have been proposed to assess inflammation and atherosclerosis in cardiology, oncology, and CKD patients (9,10). NLR is a useful predictor of mortality in HD patients (5,11). Another novel prognostic indicator in HD patients is the platelet-to-lymphocyte ratio (PLR), which measures the ratio of platelets to lymphocytes in blood with a standard range of 92.88 ± 28.70 for men and 108.02 ± 32.99 for women (7,12,13). Platelets promote inflammation and atherogenesis, making PLR a potential predictor of mortality in HD patients (14). In this study, we aim to evaluate the relationship between NLR, PLR, and their value to predict inflammatory conditions by comparing their values with hs-CRP levels as an accepted biomarker for inflammation-related cardiovascular disease (a level greater than 3 mg/dl is considered high risk). The purpose of this cross-sectional study was to investigate the levels of NLR, PLR, and hs-CRP in patients with end-stage renal disease (ESRD) undergoing HD. The study was conducted in two academic hospitals, 22-Bahman and 17-Shahrivar, in Mashhad, Iran, between 2019 and 2020. We determined a sample size of 138 patients based

on the study conducted by *Turkman et al*, assuming a 90% confidence interval and 80% study power. However, due to limited access to these patients, 100 patients with ESRD undergoing HD were included in the study (14). These patients had been diagnosed with ESRD for at least six months and had no history of pulmonary, gastrointestinal, and urinary infections within the last three months. Patients who met these inclusion criteria were selected for the study. Several exclusion criteria were applied to ensure the validity of the results. Exclusion criteria for the current study were pregnancy, infection, rheumatologic diseases, chronic infectious disorder, liver failure, recent antibiotics consumption, recent hospitalization, present Shaldon catheter, burning, and surgery. Each eligible patient provided written informed consent for participation and allowed publication of the results anonymously. Data including age, gender, HD duration (months), and etiology of renal disease were obtained from each patient's record. The most common etiologies of ESRD include diabetic nephropathy, hypertensive nephropathy, chronic glomerulonephritis, and uncertain diagnosis.

NLR and PLR are determined using complete blood count (CBC) by dividing the number of neutrophils and platelets by the number of lymphocytes. According to the study conducted by Moosazadeh et al, the optimal cut-off value for NLR was determined to be 1.7 ± 0.7 (8). In another study by Wu et al, optimal values for PLR were identified to be 92.88 ± 28.70 for males and 108.02 ± 32.99 for females (13). For the hs-CRP measurement, 3 mL of venous blood was drawn from all subjects before the HD process under sterilized conditions and sent to the laboratory. According to standard protocols, the hs-CRP levels were examined quantitatively using Pars Azmoon kit. The cut-off value for hs-CRP to stratify groups was considered to be 3 mg/dL.

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, New York, USA). The normality of the samples was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median (interquartile range 25–%75). Categorical variables were presented as frequency and percentage. We used Spearman and Pearson's tests for correlation analysis. ROC curve analysis was employed to determine the sensitivity and specificity of NLR, PLR, and hs-CRP cut-off points. The statistically significant level was set at 0.05.

Results

Table 1 shows all patients' demographics, clinical characteristics, and laboratory findings. The patients' mean age was 37.96 ± 10.29 years, and 46% of the patients were female. The mean duration of HD was 53.32 ± 50 months. Hypertension (53%), diabetes (36%), polycystic kidney disease (6%), and nephrolithiasis (3%) were the most common etiologies of CKD among patients.

Most patients (59%) had hs-CRP levels above 3 mg/L. Regarding NLR and PLR, 48% had an NLR higher than the cutoff value. Additionally, more than half of the participants (65%) had PLR less than 139. As shown in Table 2, the results of bivariate correlation analyses showed that NLR had a non-significant relationship with hs-CRP among HD patients (r = 0.014, $P = 0.893$). However, PLR had a noticeable positive correlation with hs-CRP (r = 0.241, $P = 0.016$). After categorizing patients by age, we noticed no significant correlation between hsCRP and either LNR or PLR. There was a slight positive correlation between PLR and hs-CRP in female patients. Furthermore, PLR and hs-CRP were positively correlated with HD duration of less than five years. (r = 0.375, $P = 0.001$). Beyond etiological factors, in hypertensive patients, PLR and hs-CRP were correlated inversely (r = -0.283, $P = 0.04$). Table 3 shows the correlation of NLR and PLR with hs-CRP in different subgroups.

The optimal cut-off values of NLR and PLR were 1.94 and 123.37, respectively. Table 4 shows that the specificity and sensitivity of NLR were 39% and 69%, while the specificity and sensitivity of PLR were 70.7% and 61%, respectively. Positive and negative likelihood ratios were 2.1 and 1.81 for PLR and 1.13 and 0.7 for NLR, respectively. Figure 1

Table 1. Demographic Information, Clinical Characteristics, and Laboratory Findings of the Patients

Characteristics	Value
Demographics	
Age (y), mean ± SD (min-max)	37.96 ± 10.29 (21-76)
Gender (male/female)	54/46
Hemodialysis duration (months), mean ± SD (min-max)	54.32 ± 50.00 (7-252)
Etiology of ESRD, %	
Diabetes	36
HTN	53
Nephrolithiasis	3
Polycystic kidney disease	6
Undetermined	2
Inflammatory markers	
hs-CRP (mg/L)	6.08 ± 5.70 (0.2-21.70)
Neutrophil-lymphocyte ratio, mean ± SD (min-max)	2.79 ± 1.18 (1.06-6.21)
Platelet-lymphocyte ratio, mean ± SD (min-max)	125.80 ± 57.14 (45.88-325.29)

Hs-CRP: High-sensitivity C-reactive protein, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, ESRD: end-stage renal disease, HTN: hypertension.

Table 2. The Bivariate Correlation of NLR and PLR with hs-CRP in Patients

	PLR		NLR	
	r	*P* Value	r	*P* Value
hs-CRP	0.241	0.016	0.014	0.893

Hs-CRP: high-sensitivity C-reactive protein, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio.

depicts the ROC curve, demonstrating the low sensitivity and specificity of NLR. However, the ROC curve for PLR, with an AUC of 0.65, displayed a significantly higher AUC ($P=0.01$) than NLR (AUC = 0.51).

Discussion

In the current study, we determined the predictive value of PLR and NLR as inflammation indicators among ESRD patients receiving maintenance HD. The findings revealed a positive correlation between higher PLR values and increased hs-CRP levels, while no significant correlation was observed between NLR and hs-CRP. Besides, the association of PLR with hs-CRP exhibited gender-specific differences, and female patients had a slightly significant correlation. It should be noted that among hypertensive patients and those with less than five years of HD, PLR was positively but poorly associated with hs-CRP. These findings indicate that a convenient measurement of PLR could be a useful marker to evaluate inflammation in HD patients. In line with our results, El-Hafeez et al demonstrated a positive correlation between hs-CRP and PLR (9). These results are explained considering the thrombotic effects of platelets and their involvement in atherosclerosis by secreting pro-inflammatory cytokines (15). On the other hand, Ustundag et al revealed that PLR values were significantly higher in patients with subclinical inflammation (according to mildly elevated CRP levels) than in patients with higher CRP levels (16). PLR has also been used for predicting vascular calcification resulting from cardiovascular complications and inflammation in ESRD patients (17). The study of Ahbap et al also reported findings similar to our study, which showed a significant and positive correlation of hs-CRP with NLR and PLR (though with poor sensitivity and specificity) (18). The present study did not find a correlation between NLR and hs-CRP, which is contrary to previous investigations (5, 11, 19). Since the mean age of our patients was lower than that of the participants in other studies, we assumed that age differentiation was a possible cause of the latter finding. The lack of correlation between NLR and hs-CRP in our study may be due to the fact that NLR is lower in the young population (20). Regarding the measurement of IL-6 and TNF-α levels, *Turkman et al* detected PLR as a better predictive factor for inflammation than NLR in the ESRD population, which conforms to our results (14). Alternatively, we used hs-CRP as an inflammatory indicator with substantial value in reflecting the vicious circle of malnutrition-inflammation-atherosclerosis syndrome in ESRD patients (14, 18). Data on atherosclerosis and hypertension showed raised neutrophil counts and diminished lymphocyte counts, which were common findings in CKD and led to the possible role of leukocytes in essential hypertension. Furthermore, studies suggested the relationship between higher PLR values and non-dipper hypertension (18, 21). We also found an additive relationship between PLR and hs-CRP among patients with hypertension, but we did not find any association between NLR and hs-CRP.

Evidence showed that prolonging the duration of HD might aggravate inflammation (22). Relevant studies could not find any association between the duration of dialysis and these laboratory indicators of inflammation (18).

Table 3. The Bivariate Correlation of NLR and PLR with hs-CRP in Different Groups

Groups (hs-CRP)	PLR		NLR	
	r	*P*	r	*P*
<55 years	0.297	0.051	- 0.029	0.850
≥55 years	0.212	0.117	0.043	0.754
Male	0.188	0.174	0.070	0.613
Female	0.303	0.041	0.104	0.411
<5 years on HD	0.375	0.001	-0.043	0.721
≥5 years on HD	-0.054	0.189	0.189	0.336
Diabetes	0.144	0.402	-0.106	0.144
HTN	-0.283	0.040	0.058	0.677
Nephrolithiasis	-0.500	0.667	-0.500	0.677
Polycystic kidney disease	0.114	0.111	0.143	0.787
Undetermined	-1/00	-	1/00	0.0

Hs-CRP: High-sensitivity C-reactive protein, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, HD: hemodialysis, HTN: hypertension.

Table 4. The Relationship of NLR and PLR with hs-CRP in Hemodialysis Patients

	PLR	NLR
AUC	0.65	0.51
Sensitivity (%)	61	69
Specificity (%)	70.7	39
Positive likelihood ratio	2.1	1.13
Negative likelihood ratio	1.81	0.7
Cut-off value	123.37	1.94
P value	0.01	0.8

NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, AUC: area under the curve.

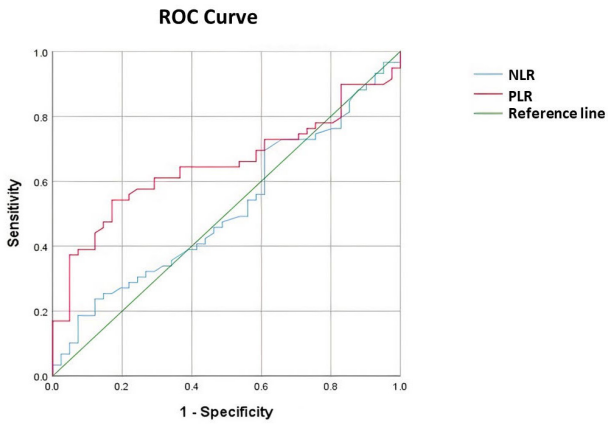

Figure 1. ROC Analysis of the Relationship between NLR, PLR, and hs-CRP

We found no correlation between hs-CRP and duration of dialysis. Nevertheless, subgroup analysis (dialysis duration of <5 and ≥ 5) showed a slightly significant correlation in patients who had dialysis duration of less than five years (higher levels of PLR and hs-CRP). In 2022, a study conducted by Wang et al demonstrated that NLR and PLR can be employed to assess the vulnerability of dialysis patients (23). Similarly, Zhang et al revealed that high levels of NLP and PLR could be associated with poor survival rates in HD patients (24). Unfortunately, our study did not assess the survival rate.

There were some limitations in the study. First, the cross-sectional design of the study prevented us from establishing cause-and-effect relationships. Second, not all well-known inflammatory markers, such as IL-6 and TNF-α, were evaluated due to financial issues and equipment limitations. Third, the sample size was relatively small; hence, further larger prospective studies with control groups in addition to HD, peritoneal dialysis, and kidney transplantation patients are required. Nevertheless, the correlation of NLR and PLR with hs-CRP in subgroups defined by age, gender, dialysis duration, and etiological factors strengthened our study.

Conclusion

In conclusion, PLR could be a convenient and cost-effective method to evaluate inflammation in ESRD patients receiving maintenance HD, especially in regions with limited financial resources, even though further studies are required to determine the correlation.

Acknowledgements

The authors would like to thank Seyed Mohamad Najarzadeh and Hosein Mokhtari for their insightful review of the manuscript.

Authors' Contribution

Conceptualization: Marzieh Kazerani.
Data curation: Fatemeh Javadi Rad, Sara Raji.
Formal analysis: Sara Raji, Mahdi Mottaghi.
Funding acquisition: Marzieh Kazerani, Fatemeh Javadi Rad.
Investigation: Marzieh Kazerani.
Methodology: Marzieh Kazerani.
Project administration: Marzieh Kazerani.
Resources: Marzieh Kazerani, Fatemeh Javadi Rad.
Software: Sara Raji.
Supervision: Marzieh Kazerani.
Validation: Marzieh Kazerani.
Visualization: Sara Raji.
Writing–original draft: Marzieh Kazerani, Sara Raji, Fatemeh Javadi Rad.
Writing–review & editing: Marzieh Kazerani, Sara Raji, Fatemeh Javadi Rad, Mahdi Mottaghi.

Competing Interests

The authors declare no conflict of interests.

Funding

None.

Ethical Approval

The present study was approved by the Medical Ethics Committee of the Islamic Azad University of Mashhad (IR.IAU.MSHD.REC.1398.102). The authors declare that they have obtained all appropriate patient consent forms. The patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal anonymously. All methods were carried out following relevant guidelines and regulations.

References

1. Zeng M, Liu Y, Liu F, Peng Y, Sun L, Xiao L. J-shaped association of platelet-to-lymphocyte ratio with 5-year mortality among patients with chronic kidney disease in a prospective cohort study. Int Urol Nephrol. 2020;52(10):1943-57. doi: 10.1007/s11255-020-02548-1.
2. Senevirathna L, Abeysekera T, Nanayakkara S, Chandrajith R, Ratnatunga N, Harada KH, et al. Risk factors associated with disease progression and mortality in chronic kidney disease of uncertain etiology: a cohort study in Medawachchiya, Sri Lanka. Environ Health Prev Med. 2012;17(3):191-8. doi: 10.1007/s12199-011-0237-7.
3. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999;55(2):648-58. doi: 10.1046/j.1523-1755.1999.00273.x.
4. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2000;35(3):469-76. doi: 10.1016/s0272-6386(00)70200-9.
5. Malhotra R, Marcelli D, von Gersdorff G, Grassmann A, Schaller M, Bayh I, et al. Relationship of neutrophil-to-lymphocyte ratio and serum albumin levels with C-reactive protein in hemodialysis patients: results from 2 international cohort studies. Nephron. 2015;130(4):263-70. doi: 10.1159/000437005.
6. Boenisch O, Ehmke KD, Heddergott A, Naoum C, Frei U, Schindler R. C-reactive-protein and cytokine plasma levels in hemodialysis patients. J Nephrol. 2002;15(5):547-51.
7. Li P, Xia C, Liu P, Peng Z, Huang H, Wu J, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in evaluation of inflammation in non-dialysis patients with end-stage renal disease (ESRD). BMC Nephrol. 2020;21(1):511. doi: 10.1186/s12882-020-02174-0.
8. Moosazadeh M, Maleki I, Alizadeh-Navaei R, Kheradmand M, Hedayatizadeh-Omran A, Shamshirian A, et al. Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: results of Tabari cohort. Caspian J Intern Med. 2019;10(3):320-5. doi: 10.22088/cjim.10.3.320.
9. Abd El-Hafeez A, Al-Alashkar AM, Abo Mohamed NM, Khalil Zoheir MI. Association between neutrophil to lymphocyte ratio and inflammatory markers in hemodialysis patients. Egypt J Hosp Med. 2019;77(5):5681-9. doi: 10.21608/ejhm.2019.62671.
10. Ohno Y, Nakashima J, Ohori M, Hatano T, Tachibana M. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. J Urol. 2010;184(3):873-8. doi: 10.1016/j.juro.2010.05.028.
11. Okyay GU, İnal S, Öneç K, Er RE, Paşaoğlu Ö, Paşaoğlu H, et al. Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail. 2013;35(1):29-36. doi: 10.3109/0886022x.2012.734429.
12. Saberi A, Bijari M, Eshraghi A. The prognostic value of platelet-to-lymphocyte ratio in patients with acute coronary syndrome: a systematic review and meta-analysis. Med J

Mashhad Univ Med Sci. 2019;61(6):1264-78. doi: 10.22038/mjms.2019.13471. [Persian].
13. Wu L, Zou S, Wang C, Tan X, Yu M. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in Chinese Han population from Chaoshan region in South China. BMC Cardiovasc Disord. 2019;19(1):125. doi: 10.1186/s12872-019-1110-7.
14. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17(3):391-6. doi: 10.1111/hdi.12040.
15. Taymez DG, Ucar E, Turkmen K, Ucar R, Afsar B, Gaipov A, et al. The predictive value of platelet/lymphocyte ratio in hemodialysis patients with erythropoietin resistance. Ther Apher Dial. 2016;20(2):118-21. doi: 10.1111/1744-9987.12380.
16. Ustundag Y, Huysal K, Gecgel SK, Unal D. Relationship between C-reactive protein, systemic immune-inflammation index, and routine hemogram-related inflammatory markers in low-grade inflammation. Int J Med Biochem. 2018;1(1):24-8. doi: 10.14744/ijmb.2017.08108.
17. Chandra A, Raj G, Awasthi NP, Rao N, Srivastava D. Evaluation of the relationship between blood cell parameters and vascular calcification in dialysis-dependent end-stage renal disease patients. Saudi J Kidney Dis Transpl. 2020;31(1):136-43. doi: 10.4103/1319-2442.279933.
18. Ahbap E, Sakaci T, Kara E, Sahutoglu T, Koc Y, Basturk T, et al. Neutrophil-to-lymphocyte ratio and platelet-tolymphocyte ratio in evaluation of inflammation in end-stage renal disease. Clin Nephrol. 2016;85(4):199-208. doi: 10.5414/cn108584.
19. Zahed NS, Karimi Mahali Z. Evaluation of cutoff point and power of neutrophil to lymphocyte ratio in diagnosing chronic inflammation in end-stage renal disease (ESDR) patients. Med J Mashhad Univ Med Sci. 2015;58(6):289-94. doi: 10.22038/mjms.2015.5000. [Persian].
20. Li J, Chen Q, Luo X, Hong J, Pan K, Lin X, et al. Neutrophil-to-lymphocyte ratio positively correlates to age in healthy population. J Clin Lab Anal. 2015;29(6):437-43. doi: 10.1002/jcla.21791.
21. Bayrakci N, Ozkayar N, Akyel F, Ates I, Akyel S, Dede F. The platelet-to-lymphocyte ratio as an inflammation marker in non-dipper hypertensive patients. Hippokratia. 2015;19(2):114-8.
22. Zuo C, Qiu HY, Li Z, Xie XS, Fan JM. [Relationship between cardiovascular complication and inflammation, oxidative stress of patient with maintenance hemodialysis]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2008;39(1):119-21. [Chinese].
23. Wang J, Huang L, Xu M, Yang L, Deng X, Li B. Study on the clinical implications of NLR and PLR for diagnosing frailty in maintenance hemodialysis patients and their correlations with patient prognosis. J Healthc Eng. 2022;2022:1267200. doi: 10.1155/2022/1267200.
24. Zhang J, Lu X, Wang S, Li H. High neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are associated with poor survival in patients with hemodialysis. Biomed Res Int. 2021;2021:9958081. doi: 10.1155/2021/9958081.