The Benefit of Neutrophil to Lymphocyte Ratio vs Platelet to Lymphocyte Ratio as New Indicators of Erythropoietin Resistance in Patients Receiving Hemodialysis

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ABSTRACT

Background: Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have emerged as promising markers in assessing erythropoietin (EPO) resistance among hemodialysis (HD) patients

Objective: The purpose of this study was to explore the potential of the PLR and NLR as indicators of how HD patients respond to erythropoiesis-stimulating agents (ESAs), and to see if PLR and NLR could help predict which patients might have trouble responding to ESA treatment. **Patients and Methods:** This was a prospective study involving 100 HD male and female patients over the age of 18 years. The patients were divided into two groups: Group I (n=47) included patients resistant to ESAs, and Group II (n=53) included patients responsive to ESAs.

Results: Both PLR and NLR were inversely correlated with hemoglobin levels after three months of ESAs treatment and positively correlated with each other. PLR and NLR had nonsignificant correlations with various clinical and biochemical parameters. According to the PLR and NLR to differentiate EPO resistance in HD patients from non-EPO resistance in HD patients respectively, at a cut-off value of ≥ 44.98 and0 .835, the sensitivity was 91.5% and 89.4%, the specificity was 77.4% and 62.3%. Erythropoietin resistance index (EHRI), PLR and NLR were significantly correlated with the prediction of EPO resistance in HD patients. EHRI, PLR and NLR were significantly high between both groups.

Conclusions: PLR and NLR could help in assessing both inflammation and EPO resistance in HD patients. Combining these two measures might make it easier to identify patients who need higher ESA doses.

Keywords: PLR, NLR, Erythropoietin, Hemodialysis**.**

INTRODUCTION

Maintenance HD has become the primary form of renal replacement therapy for individuals with ESRD [1]. As life expectancy improves for these patients due to advancements in dialysis technology and clinical care, they increasingly face complex metabolic challenges. Notably, disturbances in phosphorus (Po4) and calcium (Ca) metabolism, enhanced energy and protein demands, and muscle wasting are common [2]. These issues heighten the risk of developing anemia and frailty, two of the most prevalent complications associated with CKD. The prevalence of these conditions is closely tied to a greater burden of comorbidities and an elevated risk of mortality [3]. Anemia in ESRD is primarily attributed to a deficiency of EPO, a hormone produced by the kidneys that stimulates red blood cell production. However, multiple factors contribute to anemia in this population. These include inadequate dialysis, hyperparathyroidism, iron deficiency, occult blood loss, and deficiencies in vitamin B12 and folate, all of which may exacerbate the severity of anemia. Importantly, the degree of anemia in ESRD is often correlated with the severity of kidney dysfunction, and it significantly impairs quality of life by contributing to fatigue, weakness, and reduced exercise tolerance[4].

The introduction of ESAs has markedly improved the management of anemia in ESRD. These agents, which mimic the action of endogenous EPO, have led to a reduction in the need for blood transfusions and have contributed to a decline in mortality rates among dialysis patients. However, a significant challenge in the clinical management of ESRD-related anemia is "EPO resistance." This phenomenon, where patients fail to respond adequately to ESA treatment, is associated with a poorer prognosis, including higher rates of cardiovascular complications, hospitalizations, and mortality [5]. A study conducted by **Wish *et al.*** [6] defines ESA hyporesponsiveness as the inability to reach the desired Hb concentration of more than 11 g/dl in patients receiving weekly doses of ESAs equivalent to more than 500 IU/kg epoetin, or in patients who require such large dosages to maintain the goal for an extended period of time. The PLR and NLR are newly identified biological indicators of inflammation and endothelial dysfunction [7]. Research shows that certain types of white blood cells can predict mortality, inflammation, and tissue damage better than the total white blood cell count. In people with ESRD, a higher white blood cell count is linked to a greater risk of heart-related death, especially in those with low hemoglobin. This risk is even higher when looking at the NLR, which compares two types of white blood cells. A higher NLR has been linked to worse outcomes, like more heart problems and higher overall death rates. This makes NLR a useful tool for assessment risks in ESRD patients [8]. This study was out to test PLR and NLR as novel indicators for determining the responsiveness of ESAs in individuals with HD.

Received: 07/07/2024
Accepted: 05/09/2024

PATIENTS AND METHODS

This prospective cohort study included a total of 100 patients, both sexes, aged > 18 years, who were receiving regular HD at Dialysis Units, Tanta University Hospitals. This study was conducted between September 2023 to March 2024.

Exclusion criteria: Patients with a history of iron deficiency, current infection, hematologic disorders (such as sickle cell disease, b-thalassemia, autoimmune hemolytic anemia (AIHA), glucose 6-phosphate dehydrogenase deficiency (G6PD) and pure red cell aplasia (PRCA), hematologic malignancies, a history of recent hospital stays, blood transfusions, and steroid medication.

Patients were allocated into two groups: **Group I** (n=47): 26 males and 21 females undergoing regular HD on ESAs but with ESAs resistance, as shown by follow up lab results after 3 months of ESAs treatment. A poor response to ESAs in HD patients is characterized by the inability to achieve or maintain target hemoglobin levels (10-11.5 g/dL) despite escalating ESAs doses, suggesting resistance and **group II** (n=53): 29 males and 24 females undergoing regular HD on ESAs treatment with good response to it, as shown by follow up lab results after 3 months of ESAs treatment. A good response to ESAs in HD patients is defined by achieving and maintaining Hb levels within the target range of 10- 11.5 g/dL without necessitating an increase in the ESAs dosage. Complete blood counts (CBC), renal function tests (blood urea, creatinine, blood urea nitrogen (BUN), calcium, parathormone hormone (PTH), serum albumin, serum iron and ferritin, transferrin saturation (TSAT), and lipid profiles were performed on all patients. Additionally, a clinical examination and laboratory investigations were conducted on all patients. The HD was administered three times weekly, with each session lasting four hours. The dialysis employed a blood flow rate of 250 to 300 mL per minute and a dialysate flow rate of 500 mL/min, utilizing a Fresenius dialysis machine and a high-flux Allmed filter. All participants were also receiving treatment with ESAs.

Blood collection and processing: After a six-hour fast, a 10-milliliter venous blood sample was taken in plain vaccutainer tubes in accordance with quality control and safety procedures; two centimetres were added to EDTA for CBC. The CBC was performed using a microscopic analysis of peripheral blood smears stained with Giemsa stain on a SYSMEX cell counter, xn-10, located in Kobe, Japan. For each specimen, serum was extracted from the remaining 8 cm of blood using fine centrifugation for 15 minutes at 3000 rpm. Within two hours of collection, serum samples were submitted to the lab for examination.

Calculation of the NLR, PLR and EPO hypo responsiveness index:

NLR, or the ratio of the blood count's absolute neutrophil to absolute lymphocyte counts, was computed. PLR, or the ratio of the absolute lymphocyte count in the blood count to the platelet count, was computed. The EHRI was calculated by dividing the weekly EPO dose (IU) by the dry weight (kg) and then by the blood Hb levels (g/dl). Body weight, Hb, and the average 6-month EPO dosage were employed in this computation.

Ethical approval: This study was ethically approved by the Tanta University Hospitals' Ethical Committee, Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis: Version 26.0 of SPSS was used to perform the statistical analysis. The data's normality was validated using the Shapiro-Wilks test and histogram analysis. The two groups were compared using the unpaired Student's t-test for quantitative parametric variables with reported mean± SD. A Mann Whitney test was used to assess non-parametric data that were presented as IQR and median. To analyze the frequency and percentage (%) of qualitative variables, either the X^2-test or Fisher's exact test was employed, depending on its relevance. To ascertain the link between various variables, the Pearson moment correlation equation was employed. One independent variable and the dependent variable were shown to be related using the univariate regression model. Multivariate regression was used to ascertain the association between the dependent and several independent variables, and the ROC curve was used to evaluate sensitivity, specificity, positive predictive value, and negative predictive value. A two-tailed test is considered statistically significant if the P value is less than 0.05.

RESULTS

Table 1 shows the demographic and laboratory data among the study population.

Table (1): Demographic and laboratory data among the study population

		N=100
Age (years)		50.43±16.32
Sex	**Male**	55 (55.0%)
	Female	45 (45.0%)
Duration of HD (Years)		7 (10–3)
Dry weight (Kg)		82.37±15.71
Triglycerides (mg/dL)		150.7±30.51
LDL (mg/dL)		170.7±25.77
Hb after 3 months of ESAs treatment (g/dL)		9.6±2.4
PLTs ($\times 10^9$ /L)		197.73±48.9
WBCs ($\times 10^9$ /L)		6 (8.1–4.63)
PLR		85.38 (139.67–53.14)
NLR		1.57 (2.32–0.83)
Urea (mg/dL)		68.17±15.79
Creatinine (mg/dL)		6.95±1.60
BUN (mg/dL)		32.51±7.84
Total Calcium (mg/dL)		9.92±1.92
Ionized Calcium (mg/dL)		1.25±0.25
Po_4 (mg/dL)		4.551 (5.75–3.25)
PTH (pg/dL)		301 (544–151.25)
Serum albumin (g/dL)		4 (4.2–3.5)
Serum Iron (ug/dL)		62±14.9
TSAT (%)		25 (30.08–19.0)
Serum ferritin (ng/mL)		682 (948.75–382)

Median and range: nonparametric test., HD: hemodialysis, LDL: low density lipoprotein, Hb: hemoglobin, ESAs: erythropoiesis-stimulating agents, WBCs: white blood cells, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, BUN: blood urea nitrogen, Ca: calcium, Po_4: phosphorus, PTH: parathormone hormone, TSAT: transferrin saturation, P: Platelets.

Demographic data, etiology of ESRD and clinical findings were insignificantly difference between the two groups (**Table 2).**

Table (2): Demographic data, etiology of ESRD and clinical findings among the studied groups

		Group I (n=47)	Group II (n=53)	P
Age		51.98±17.59	49.06±15.15	0.374 [(a)]
Sex	**Male**	26 (55.3%)	29 (54.7%)	0.952 [(b)]
	Female	21 (44.7%)	24 (45.3%)	
Duration of HD (years)		5 (9-4)	7 (10-3)	0.196 [(c)]
Dry weight (kg)		82.85±16.98	81.75±14.21	0.726 [(a)]
Smoking		11 (23.4%)	11 (20.8%)	0.750 [(b)]
Etiology of CKD	**Obstructive uropathy**	6 (12.8%)	6 (11.3%)	0.518 [(b)]
	HTN	25 (53.2%)	24 (45.3%)	
	Pre-eclampsia	4 (8.5%)	5 (9.4%)	
	Congenital atrophied kidneys	3 (6.4%)	3 (5.7%)	
	Lupus nephropathy	3 (6.4%)	3 (5.7%)	
	Drug induced nephropathy	1 (2.1%)	2 (3.8%)	
	Analgesic nephropathy	0 (0.0%)	1 (1.9%)	
	Multiple myeloma	1 (2.1%)	0 (0.0%)	
	Polycystic kidney Disease	0 (0.0%)	6 (11.3%)	
	Cardiomyopathy	3 (6.4%)	3 (5.7%)	
	Post-transplantation	1 (2.1%)	0 (0.0%)	
Clinical history	**Cardiac**	9 (19.1%)	3 (5.7%)	0.063 [(b)]
	DM	9 (19.1%)	16 (30.2%)	
	HTN	13 (27.7%)	9 (17.0%)	

HD: hemodialysis, HTN: hypertension, ESRD: end stage renal disease, [(a)]: independent-sample t-test, [(b)]: chi-square test and fisher's exact, [(c)]: Mann-Whitney U test, DM: diabetes mellitus.

Lipid profile, P, urea, BUN, total, ionized Ca, PO_4, PTH, serum albumin and iron profile were insignificantly different between both groups. Hb, Hb after 3 months of ESAs treatment, WBCs and creatinine were significantly decrease between both groups. EHRI, PLR and NLR were significantly increase between both groups **(Table 3).**

Table (3): Laboratory investigations among the studied groups

		Group I (n=47)	Group II (n=53)	P
Lipid profile	**Triglycerides (mg/dl)**	153.77±28.20	148.15±32.54	0.362 (a)
	LDL (mg/dl)	173.02±28.29	168.64±23.39	0.399 (a)
CBC	**Hb (g/dl) before ESAs treatment.**	8.68±1.06	9.19±1.43	**0.043*** (a)
	Hb after 3 months of ESAs treatment (g/dL)	8.59±1.14	10.59±1.43	**<0.001*** (a)
	P (×10^9 /L)	195.32±46.93	199.87±48.44	0.782 (a)
	EHRI (UI/kg/week)	16.2 (23.3-13)	14.1 (17.5-10.95)	**0.01*** (c)
	WBCs (×10^9 /L)	5.2 (7.8-4)	6.8 (8.29-5.1)	**0.024*** (c)
	PLR	123.42 (163.89-78.24)	64.31 (92.79-46.51)	**<0.001*** (c)
	NLR	2.1 (2.69-1.37)	1.34 (1.97-0.49)	**<0.001*** (c)
Renal function tests	**Urea (mg/dL)**	66.19±15.31	69.93±16.54	0.584 (a)
	Creatinine (mg/dL)	6.49±1.60	7.35±1.70	**0.037*** (a)
	BUN (mg/dL)	31.62±7.81	33.31±8.11	0.615 (a)
Electrolytes	**Total Ca (mg/dL)**	9.87±2.01	9.97±1.87	0.790 (a)
	Ionized Ca (mmol/L)	1.27±0.23	1.23±0.19	0.448 (a)
	Po_4 (mg/dL)	4.7 (5.4–3.5)	4.5 (6.1–2.9)	0.959 (c)
PTH		268 (600-126)	312 (536-173.5)	0.595 (c)
Serum albumin (g/dl)		3.95 (4.2-3.58)	4 (4.3-3.3)	0.906 (c)
Iron profile	**Serum iron (ug/dL)**	61.61±15.12	62.37±15.30	0.849 (a)
	TSAT (%)	24 (29-17.2)	25 (33-19.5)	0.265 (c)
	Serum ferritin (ng/mL)	741 (951-439)	587 (952.5-338)	0.239 (c)

Median and range: nonparametric test, *Significant. LDL: low density lipoprotein, CBC: complete blood count, Hb: Hemoglobin, EHRI: Erythropoietin resistance index, WBCs: White blood cells, P: Platelets, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, BUN: blood urea nitrogen, Ca: calcium, Po_4: Phosphorus, PTH: parathormone, TSAT: transferrin saturation, (a): independent-sample t-test, (c): Mann-Whitney U test.

PLR was negatively correlated with Hb after 3 months of ESAs treatment and WBCs. Also, PLR was positively correlated with triglycerides, P and NLR. While, the PLR was not correlated with age, sex, duration of HD, dry weight, Hb, EHRI, LDL, urea, creatinine, BUN, total Ca, ionized Ca, Po_4, PTH, serum albumin, serum iron, TSAT, and serum ferritin. NLR was negatively correlated with Hb after 3 months of ESAs treatment. Also, the NLR was positively correlated with PLR. While, the NLR was not correlated with age, sex, duration of HD, dry weight, Hb, EHRI, P, WBCs, triglycerides, LDL, urea, creatinine, BUN, total Ca, ionized Ca, Po_4, PTH, serum albumin, serum iron, TSAT, and serum ferritin. **Table 4**

Table (4): Correlations between PLR and NLR and other parameters

	PLR		NLR	
	R	**P**	**r**	**P**
Triglycerides (mg/dL)	0.246	**0.018***	0.172	0.09
LDL (mg/dL)	-0.004	0.970	0.058	0.569
Hb (g/dL) before ESAs ttt.	-0.053	0.602	-0.130	0.198
Hb after 3 months of ESAs treatment (g/dL)	-0.369	**<0.001***	-0.449	**<0.001***
EHRI	0.107	0.288	0.185	0.065
P (×10^9 /L)	0.287	**0.004***	0.021	0.910
WBCs (×10^9 /L)	-0.347	**<0.001***	-0.067	0.505
PLR	--	--	0.437	**<0.001***
NLR	0.437	**<0.001***	--	--
Urea (mg/dL)	-0.145	0.149	0.028	0.779
Creatinine (mg/dL)	-0.115	0.256	-0.084	0.407
BUN (mg/dL)	-0.05	0.624	0.071	0.483
Total Ca (mg/dL)	-0.035	0.808	-0.029	0.775
Ionized Ca (mg/dL)	0.114	0.258	0.105	0.300
Po_4 (mg/dL)	-0.009	0.931	0.125	0.256
PTH (pg./dL)	-0.103	0.310	-0.165	0.102
Serum albumin (g/dL)	-0.068	0.499	0.045	0.660
Serum iron (ug/dL)	-0.032	0.732	-0.01	0.918
TSAT (%)	-0.133	0.186	0.131	0.193
Serum ferritin (ng/mL)	0.165	0.082	0.044	0.663

*Significant, r: Pearson and spearman correlation.

The regression analysis revealed that EHRI, PLR and NLR were significantly associated with the prediction of EPO resistance in HD patients **(Table 5).**

Table (5): Regression analysis for potential predictor factors affecting EPO resistance in HD patients

	Odds Ratio (95%) CI	P
EHRI	0.907 (0.847–0.972)	**0.005***
PLR	0.982 (0.973–0.991)	**<0.001***
NLR	0.472 (0.304–0.734)	**<0.001***

*Significant. CI: confidence intervals.

According to the PLR and NLR to discriminate EPO resistance in HD patients from non-EPO resistance in HD patients respectively, at a cut-off value of ≥ 44.98 and0 .835; the area under the curve was 0.735 and 0.720, the sensitivity was 91.5% and 89.4%, the specificity was 77.4% and 62.3%, PPV was 78.2% and67.8%, and NPV was 91.1% and 86.8% (**Figure 1).**

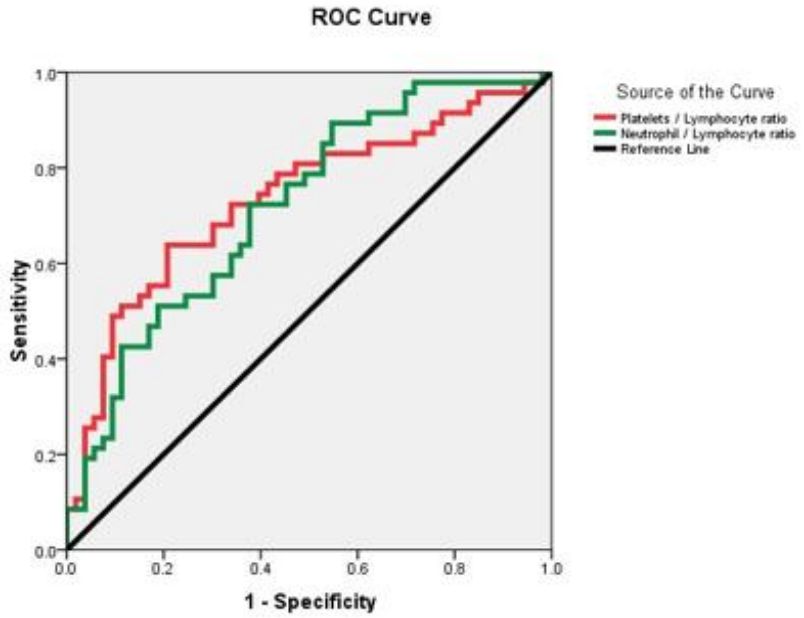

Figure (1): ROC curve of PLR and NLR to discriminate EHRI in HD patients from non- EHRI in HD patients.

DISCUSSION

EPO resistance remains a significant challenge in the management of anemia among HD patients. The investigation of hematological ratios, such as the PLR and NLR, presents a promising approach for understanding the inflammatory and metabolic disturbances that contribute to EPO resistance [8]. In this study, we identified a strong correlation between EPO resistance and serum Hb levels, further elucidating the role of these hematological parameters in the pathophysiology of anemia in HD patients.

Our findings were consistent with those of **Joksimovic Jovic *et al.* [9],** who reported that individuals with EPO resistance had significantly lower serum Hb levels. Regarding the duration of HD, the median duration in Group I was 5 years , while in Group II, the median HD duration was 7 years. There was only a minimal difference between the two groups in terms of HD duration, which aligned with the findings of **El-Shishtawy *et al.* [10],** who also observed no significant association between HD duration and EPO resistance.

In terms of platelet count, we found no significant difference between the two groups, further suggesting that platelet levels may not be directly related to EPO resistance. Our results demonstrated lower platelet counts in the EPO-resistant group compared to the non-resistant group, a finding that contrasted with the study by **Hacein-Bey-Abina *et al.* [11],** who concluded that EPO, when combined with other early-acting cytokines, has both in vivo platelet activation activity and in vitro megakaryocytic potential.

The EHRI was significantly different between the two groups, which was consistent with the findings of **El-Sheikh *et al.* [12],** who reported that individuals with EPO resistance had higher EHRI values compared to those who responded well to EPO therapy.

We also observed a statistically significant difference in the PLR between the two groups. In agreement with our results, **Taymez *et al.* [13]** showed that PLR levels increased from the 25th to the 75th

percentile when comparing patients with low and high EHRI values.

Similarly, the NLR was significantly higher in the EPO-resistant group. This finding aligns with that of **Valga *et al.*** [14], who reported that NLR is a significant predictor of EPO resistance.

In contrast, our earlier investigation showed no significant difference in **serum albumin levels** between the two groups, which is consistent with the study by **Kalantar-Zadeh *et al.*** [15] who found no association between serum albumin levels and EPO hypo-responsiveness.

Regarding the serum iron profile, including serum ferritin, TSAT, and serum iron levels, we observed no significant differences between the EPO-resistant and non-resistant groups. These finding were in line with the results of **Macdougall *et al.*** [16], who found that elevated ferritin levels, low TSAT, and reduced serum iron are indicative of functional iron deficiency rather than an absolute iron deficiency in patients with EPO resistance.

The study's findings regarding urea, creatinine, and BUN levels revealed that while there were no significant differences in urea and BUN levels between HD patients resistant to ESAs and those who were not, the ESA-resistant group had significantly lower creatinine levels compared to the non-resistant group. This observation was consistent with the explanation provided by **Feret *et al.*** [17] who attributed malnutrition in HD patients to a complex interplay of factors.

Regarding markers of CKD-MBD, no significant differences were found between the resistance and non-resistance patient groups for PTH, Po4, or ionized calcium. In agreement with our results, **Elbadawy *et al.*** [18] found no significant difference in serum calcium levels between EPO-resistant and non-resistant patients.

In this study, PLR was negatively correlated with Hb levels and WBC count after 3 months of ESA treatment. This finding was supported by **El-Hafeez *et al.*** [19], who reported that PLR had a significant positive correlation with platelet count and a significant negative correlation with Hb and WBCs. Furthermore, our findings align with those of **El-Sheikh *et al.*** [12] who found that NLR was not correlated with Hb levels after ESA treatment but was positively correlated with PLR.

In terms of predictive value, we identified optimal cutoffs for PLR and NLR in predicting EPO resistance, with values of ≥44.98 and 0.835, respectively. The AUC for these biomarkers was 0.735 for PLR and 0.720 for NLR, with a sensitivity of 91.5% and 89.4%, and specificity of 77.4%. These findings were consistent with those of **Abdel Hammed *et al.*** [20] who reported that PLR had 90% sensitivity and 70% specificity for predicting EPO response, with an overall accuracy of 82% and AUC of 0.79. Similarly, **Sheikh *et al.*** [21] found that PLR exhibited 93% sensitivity and 80-82% specificity, supporting the robustness of PLR as a predictive marker in our study.

One of the study's limitations was the very small sample size. There was just one centre for the study. So, we recommended that incorporate the PLR and NLR into diagnostic protocols for EPO resistance in HD patients to enhance diagnostic specificity and precision. Evaluate the use of PLR and NLR in conjunction with other biomarkers to improve diagnostic accuracy and understanding of EPO resistance. Proper management EPO resistance in HD, ensure optimal iron status, manage inflammation and secondary hyperparathyroidism, enhance dialysis adequacy, adjust ESAs dosing and consider new lines of treatment as HIF-PHIs for refractory cases.

CONCLUSION

It could be concluded that that the **PLR** and **NLR** hold promise as biomarkers for identifying **EPO resistance** in HD patients. Both PLR and NLR are significantly associated with inflammatory and hematological processes that may influence the response to EPO therapy. Notably, the platelet count and NLR exhibit a positive correlation with PLR, while showing a negative correlation with Hb levels and WBC counts. These findings underscore the potential of PLR and NLR as practical, non-invasive, and cost-effective biomarkers for assessing EPO resistance in clinical practice. By providing a simple and readily accessible means of evaluating inflammation and its impact on EPO response, both ratios could aid in the optimization of anemia management in HD patients. However, further research is required to validate these biomarkers and explore their integration into personalized treatment strategies aimed at improving patient outcomes.

Financial support and sponsorship: Nil
Conflict of Interest: Nil

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