The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4583-4589

Usefulness of Platelet to Lymphocyte Ratio as a marker of Erythropoietin Resistance in Hemodialysis Patients

Haitham ELSheikh[1], Ayman Fathy[1], Mona Khaled Azab[2]*, Ahmed Embaby[1]
[1]Clinical Hematology Unit, Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt
[2]Department of Internal Medicine, Al-Ahrar Hospital, Zagazig, Egypt
***Corresponding author:** Mona Khaled Azab, **Mobile:** (+20)1018646141, **E-Mail:** monaazab93@gmail.com

ABSTRACT

Background: Chronic inflammation was associated with the hyporesponsiveness to erythropoiesis stimulating agents (ESA) in hemodialysis (HD) patients. A rising indicator of inflammation is the platelet-to-lymphocyte ratio (PLR).
Objective: The aim of the current work was to assess the role of the PLR in detection of the response to ESA in HD cases.
Patients and methods: This cross-sectional study included a total of 80 patients who underwent regular HD at the Department of Internal Medicine, Zagazig University Hospitals. Patients were classified according to median value of erythropoietin hyperresponsiveness index (EHRI) into two groups: **Group1**; included (41 patients) with low resistance EHRI < 0.167, and **Group 2:** included (39 patients) with high resistance ≥ 0.167. PLR was assessed in both groups.
Results: PLR best cutoff value derived from ROC curve to predict EPO resistance was ≥87.5, with specificity, and sensitivity, were 51.3%, and 56.1%, respectively. PLR had significant positive linear correlation with MCH, MCHC, PLR platelet count, serum sodium and creatinine clearance. PLR was negatively correlated with ALC, AMC, serum creatinine, potassium, and LDL cholesterol, serum iron and TIBC. However, in multivariate linear regression analysis only ALC, platelet count, TIBC and MHCH were found to be independent determents of PLR in HD case.
Conclusion: Despite being a simple widely available marker of inflammation, PLR did not appear to be useful in reflecting the EHRI in CKD patients. Thus, we recommend further future multicenter and nationwide studies to stand on the suitable marker for EHRI in CKD population in Egypt.
Keywords: Erythropoietin Resistance, Platelet to Lymphocyte Ratio, Hemodialysis

INTRODUCTION

Patients who had chronic kidney disease (CKD) often experience anemia, a condition that is linked to higher rates of hospitalization and mortality. Anemia and erythropoietin (EPO) resistance may result from iron deficiency, occult blood loss, vitamin B12 and folate deficiencies, hemoglobinopathies, insufficient dialysis, hyperparathyroidism, and chronic inflammation. However, the relative lack of EPO secretion from the damaged kidney is the primary cause of anemia in CKD. Subsequently, anemia with CKD is typically treated with EPO therapy **(1).**

About 10% of patients had inadequate response to erythropoiesis stimulating drugs (ESA), a phenomenon known as ESA resistance. When an increased dose of an ESA is not sufficient to attain or maintain the desired hemoglobin (Hb) or hematocrit levels, this phenomenon is known as ESA resistance **(2).**

The weekly dose of EPO divided by per kilogram of body weight divided by Hb level (g/dL) has been found to be an effective index of EPO resistance; this index is known as the ESA hyporesponsiveness index (EHRI). The EHRI has a direct correlation to comorbidity and mortality in HD patients and may be easily measured in the clinic **(3).**

It has been suggested that inflammation plays a significant role in ESA hyperresponsiveness along with oxidative stress commonly occurring in uremic patients **(2).** In HD patients, inflammation was linked to a low platelet-to-lymphocyte ratio (PLR) **(4).** Thus, within the scope of these findings we aimed for assessment of PLR role for detection of the ESA hyporesponsiveness in HD cases.

PATIENTS AND METHODS

This cross-sectional study included a total of 80 patients who underwent regular HD at the Department of Internal Medicine, Zagazig University Hospitals.

Inclusion criteria: all patients aged ≥ 18 years of both sexes, who underwent HD treatment three times/ week, each at least about four hours for three months employing high permeability polyether sulfone hemodialysis filters with a surface area higher than 1.7 m^2 and an ultrafiltration rate greater than 74 ml/h/mmHg; blood flow rates of 300-400 mL/min; standard bicarbonate dialysis solution; arterial blood pressures of greater than 74 mmHg **(5),** using the erythropoiesis-stimulating agent; Epoetin Beta.

Exclusion criteria: pregnant females or patients with iron deficiency (who had serum ferritin equals or less than ng\ml that indicated the presence of iron deficiency anemia with reference to KDIGO guidelines), who had previously undergone kidney transplantation, or recent infection, or receiving immunosuppressive drugs or had history of malignancy or recently received blood transfusion.

Patients were classified according to median value of erythropoietin hyperresponsiveness index (EHRI) into two groups: **Group1**; included (41 patients) with low resistance EHRI < 0.167, and **Group 2:** included (39 patients) with high resistance ≥ 0.167.

All patients were subjected to full history taking,

Received: 22/11/2022
Accepted: 24/01/2023

clinical examination, and laboratory investigations included: Iron profile (total iron binding capacity (TIBC), serum iron, ferritin, and transferrin saturation), complete blood count (CBC), renal function tests (blood urea nitrogen, serum creatinine, creatinine clearance, urea reduction ratio), electrolytes (total and ionized calcium, phosphorus, sodium, potassium), C-reactive protein, parathyroid hormone, and Lipid profile (total cholesterol, triglycerides, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol)

Calculation of The PLR and EHRI

Patients whose Hb levels were below 11 g/dl while receiving EPO doses of 20,000 IU or more were considered to be, erythropoietin resistant [(5)]. The EHRI was determined by dividing the total weekly erythropoietin dose (in international units) by the patient's body weight (in kilograms) and then by their Hb concentration (in grammes per deciliter of blood). (5) The body weight at the end of three months of EPO treatment was used in this calculation. By dividing the total number of platelets by the total number of lymphocytes in a blood sample, the platelet to lymphocyte ratio (PLR) can be calculated [(5)].

***Ethical Consideration*:**

This study was ethically approved by Zagazig University's Research Ethics Committee (ZU- IRB #9113/23-11-2021). 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

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Categorical variables were described using their absolute frequencies and were compared using chi square test, fisher exact and Monte Carlo tests when appropriate. To compare ordinal data between two groups, chi square for trend test was used. Shapiro-Wilk test was used to verify assumptions for use in parametric tests. Quantitative variables were described using their means and standard deviations or median and range according to type of data. To compare quantitative data between two groups, independents sample t test (for normally distributed data) and Mann Whitney test (fir not normally distributed data) were used. To assess strength and direction of correlation between two continuous variables, Spearman rank correlation coefficients (for not normally distributed data) was used. To compare quantitative data between two groups, Kruskal-Wallis test (for not normally distributed data) and one way ANOVA test (for normally distributed data) were used. when the difference is significant, pairwise comparison and Tukey HSD comparison were used to detect difference between each two individual groups. ROC curve was used to determine beast cutoff of certain quantitative parameter in diagnosis of certain health problem. Binary logistic regression was used to identify independent risk factors associated with certain health problem. Linear regression analysis was performed to measure associated independent factors for dependent factor. The level statistical significance was set at $P<0.05$. A highly significant difference was present if $p\leq 0.001$

RESULTS

Baseline characteristics

This study included 80 patients on HD, out of them 67.5% were males, 66.3% were non-smokers. The mean age was 51.1 years. Fifteen patients had positive family history of CLD, 25% were diabetics, 68.8% were hypertensive, 35% had CLD, 3.8% had COPD, 40% had cardiac comorbidity, 36.3% had positive HCV and 2.5% had positive HBV. Concerning the cause of dialysis, 38.8% had hypertension as underlying cause while 16.3% and 13.8% had causes related to chronic glomerulonephritis and drug induced respectively.
According to median value of EHRI, 51.3% values more than or equal median (0.167) which was considered EPO resistant (Table 1).

Table (1): Clinico-demographic data of the study population

Parameter	N=80 (%)
Sex:	
· Female	26 (32.5%)
· Male	54 (67.5%)
Smoker:	
· Non-smokers	53 (66.3%)
· Current smoker	13 (16.3%)
· Ex-smoker	14 (17.5%)
	Mean ± SD
Age (year)	51.14 ± 13.4
Positive family history	15 (18.8%)
• Co-morbidities	
Diabetes	20 (25%)
Hypertension	55 (68.8%)
CLD	28 (35%)
COPD	3 (3.8%)
Cardiac	32 (40%)
Other	3 (3.8%)
Positive HCV	29 (36.3%)
Positive HBV	2 (2.5%)
• Cause of CKD	
Idiopathic	6 (7.5%)
Diabetes	3 (3.8%)
Hypertension	31 (38.8%)
Chronic GN	13 (16.3%)
Drug-induced	11 (13.8%)
Immune	6 (7.5%)
Miscellaneous	10 (12.5%)

CLD; chronic liver disease, COPD; Chronic obstructive pulmonary disease, HCV; hepatitis C virus, HBV; hepatitis B virus, GN ; Glomerulonephritis

EPO resistance was significantly associated with all of hemoglobin, hematocrit, RBCs, (all were significantly higher among EPO low resistance patients), while it did not have significant relation to any of other CBC parameters (Table 2).

Table (2): Association between EPO resistance and CBC-parameters:

	EPO Low Resistance **EHRI¥** 0.09 (0.06 –0.11)	**EPO High Resistance** **EHRI¥** 0.25 (0.2 – 0.29)	**P value**
WBCs (x10^3/UL)	**7.32** ± 1.8	6.9 ± 1.7	0.39
ANC (x10^3/UL)	4.64 ± 1.1	4.57 ± 1.09	0.86
ALC¥ (x10^3/UL)	1.8 (1.3 – 2.3)	1.8(1.25 – 2.2)	0.72
Hemoglobin (g/dl)	11.66 ± 1.73	10.04 ± 1.49	**<0.001****
Hematocrit (%)	36.34 ±7.82	30.99 ± 4.57	**<0.001****
RBCs (x10^6/UL)	4.16 ± 0.69	3.73 ± 0.72	**0.008***
MCV (fl)	14.78 ± 3.09	14.89 ± 2.52	0.86
MCH (PG)	85.57 ± 7.64	84.04 ± 9.05	0.42
MCHC	28.27 ± 3.16	27.81 ± 3.76	0.55
Platelet (x10^3/UL)	32.94 ± 1.48	32.67 ± 1.38	0.41
RDW (%)	213.68 ± 51.2	181.59 ± 44.21	**0.025***
PDW	12.84 ± 2.69	14.66 ± 3.2	0.10
MPV (FL)	10.67 ± 1.17	11.4 ± 0.78	0.07
PLR¥	84.74(52.63 – 132.4)	88.33(65.71 – 128.11)	0.79

¥Non-parametric data is represented as median (range) and compared using Mann-Whitney test.

Diagnostic performance of PLR

PLR best cutoff value for predicting EPO resistance is ≥87.5 and area under curve was 0.517, with specificity, sensitivity, positive predictive value, and negative predictive value were 51.3%,56.1%, 52.6%, and 54.8% respectively with overall accuracy of 53.8% (p>0.05). (Table 3, Figure 1)

Table (3): Performance of PLR in diagnosis of EPO resistance:

Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
≥87.5	0.517	51.3%	56.1%	52.6%	54.8%	53.8%	0.79

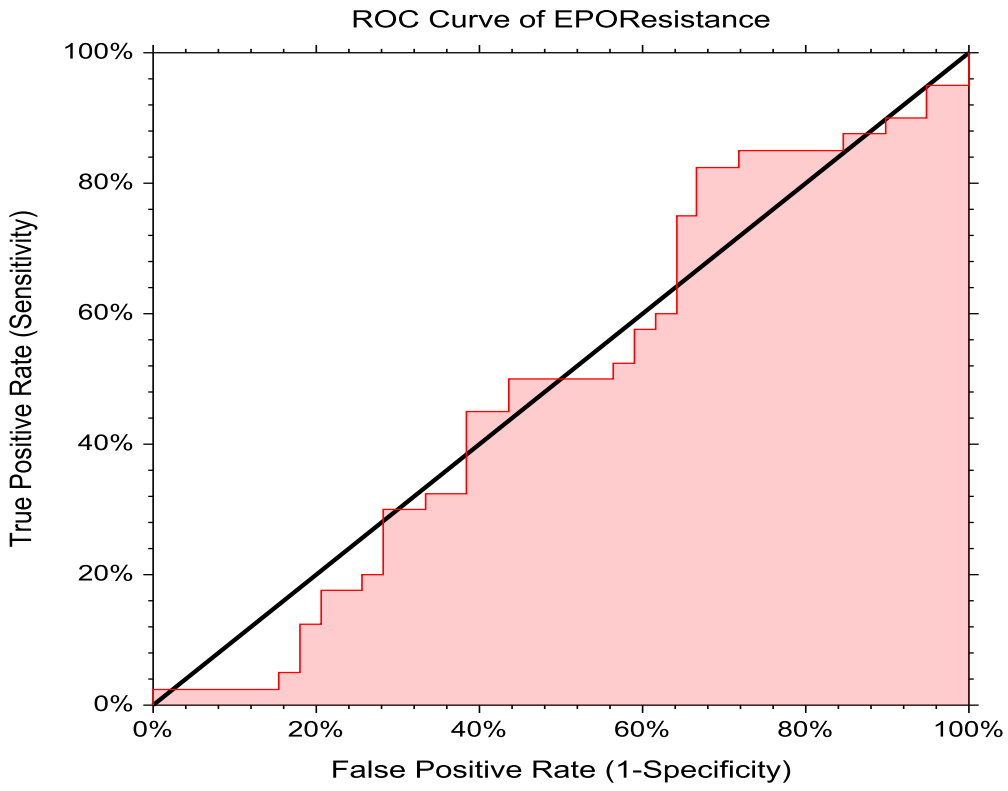

Figure (1): ROC curve showing Performance of PLR in diagnosis of EPO resistance.

Linear correlations with PLR and other parameters

PLR had significant positive correlation with MCH, MCHC, PLR platelet count, serum sodium and creatinine clearance. However, PLR was significantly correlated with all ALC, AMC, serum creatinine, potassium, and LDL cholesterol, serum iron and TIBC. Non-significant correlation was found between PLR among studied patients and either dose of erythropoietin, Kt/V or hemodialysis duration (Table 4, Figures 2 and 3).

Table (4): PLR correlation with studied parameters

	r	p
Age (year)	0.02	0.84
BMI (kg/ m^2)	-0.03	0.92
Surface area (m^2)	0.01	0.96
Smoking duration (year)	-0.03	0.92
WBCs (x10^3/UL)	-0.20	0.08
ANC (x10^3/UL)	-0.08	0.48
ALC¥ (x10^3/UL)	-0.33	0.003*
Hemoglobin (g/dl)	0.12	0.30
Hematocrit (%)	0.11	0.35
RBCs (x10^6/UL)	-0.07	0.54
MCV (fL)	0.17	0.14
MCH (PG)	0.23	0.043*
MCHC	0.28	0.011*
Platelet (x10^3/UL)	0.27	0.015*
RDW (%)	-0.21	0.07
PDW	-0.29	0.12
MPV	-0.21	0.25
BUN (mg/dl)	-0.01	0.96
Creatinine (mg/dl)	-0.23	0.04*
PTH¥ (pg/ml)	0.03	0.80
CRP¥ (mg/dl)	-0.11	0.33
Total cholesterol(mg/dl)	0.08	0.47
Triglycerides (mg/dl)	0.25	0.028*
LDL (mg/dl)	-0.33	0.003*
HDL (mg/dl)	0.10	0.36
Creatinine clearance(ml/min)	0.33	0.004*
Urea reduction ratio	0.09	0.42
Serum ferritin(ug/dl)	0.42	0.001**
TIBC (ug/dl)	-0.44	<0.001**
Serum iron(ng/dl)	-0.32	0.004*
Transferrin saturation%	-0.11	0.33
ERHI	0.006	0.985
Dose of EPO\week	-0.07	0.53
HD duration (year)	-0.04	0.70

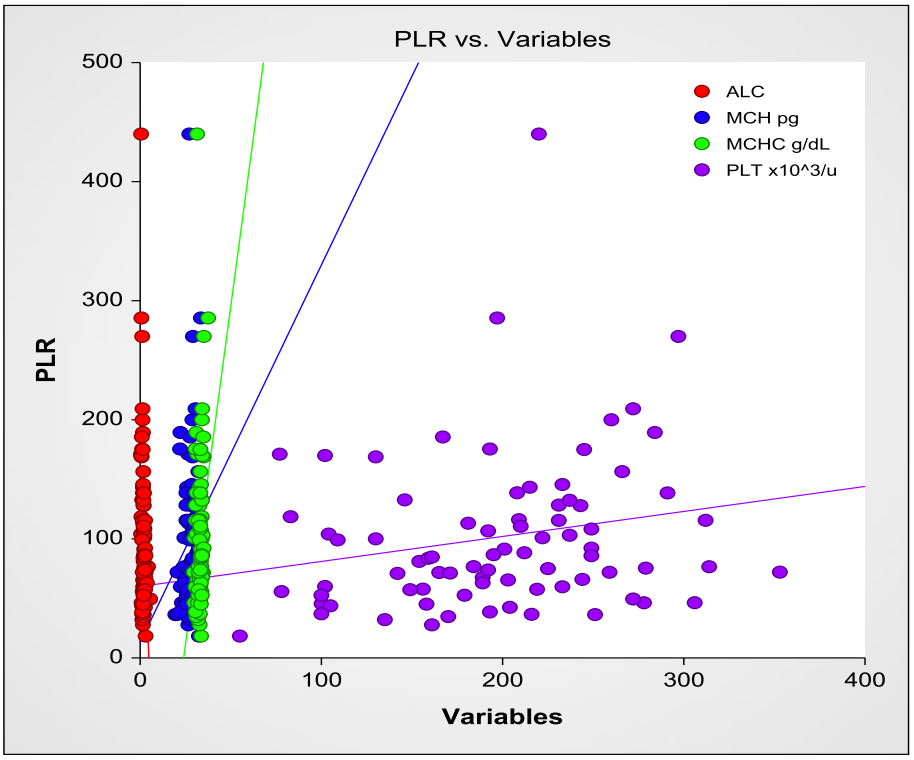

Figure (2): PLR correlation with selected CBC-parameters among the studied population

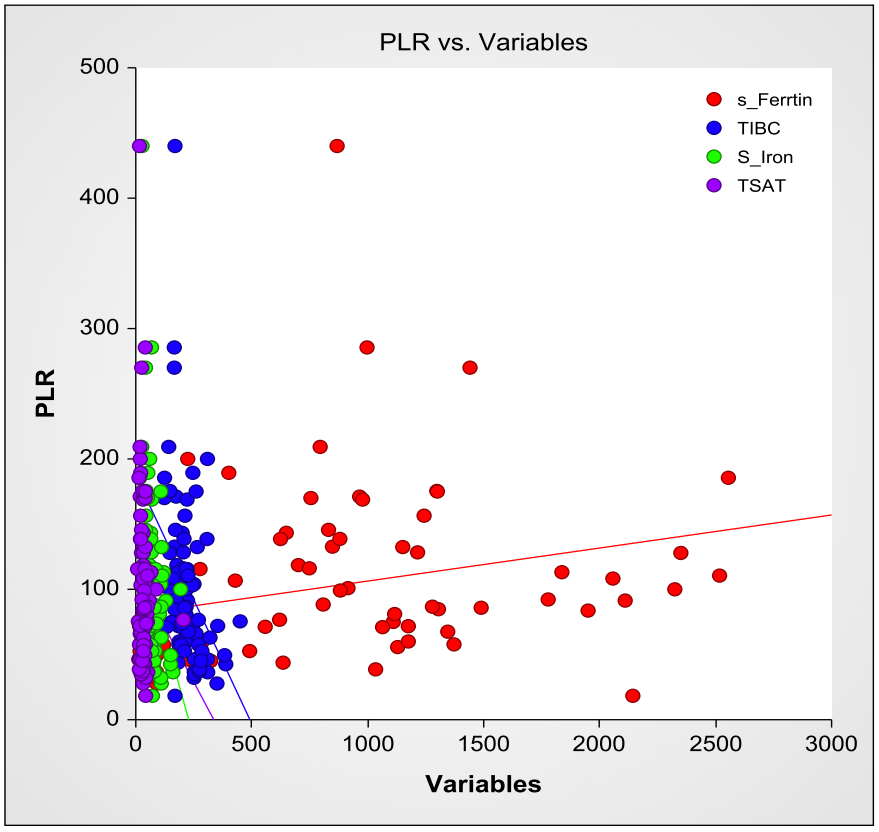

Figure (3): PLR correlation with iron profile among the studied population

Linear regression analysis of determinants of PLR

Among factors significantly correlated to PLR, multivariate analysis revealed that ALC (unstandardized β=-40.766), platelet count (unstandardized β=0.563), TIBC (unstandardized β=-0.343) and MHCH (unstandardized β=11.843) significantly independently associated with it (Table 5).

Table (5): Linear stepwise regression analysis of factors significantly associated with PLR

Covariate	Unstandardized Coefficients		Standardized Coefficients	t	P	95% Confidence Interval	
	β	Std. Error	Beta			Lower	Upper
(Constant)	-245.8	136.7		-1.798	0.076	-518.2	26.501
ALC	-40.7	6.9	-0.52	-5.87	<0.001	-54.6	-26.93
Platelet count	0.56	0.09	0.547	6.059	<0.001	0.378	0.748
TIBC	-0.34	0.09	-0.329	-3.699	<0.001	-0.528	-0.158
MCHC g/dL	11.8	3.9	0.256	3.019	0.003	4.028	19.658

DISCUSSION

As uremia leads to inhibition of erythropoiesis, shorter red blood cell (RBCs) survival, and nutritional deficits, anemia significantly impacts the quality of life of CKD patients [8]. Despite having adequate iron stores, CKD patients might become resistant to EPO for a variety of reasons, including: inflammation, poor dialysis, hyperparathyroidism, malnutrition, as well as infection [10].

Systemic inflammation can be assessed by the platelet-lymphocyte ratio (PLR) that acts as a prognostic biomarker for many diseases such as inflammatory, hematological, cardiovascular, psychiatric diseases and cancer [11]. Also, PLR was found to be an accessible predictor of COVID-19 infection mortality and its associated complications [12, 13]. Subclinical inflammation in schizophrenia was also independently associated with PLR. Schizophrenic patients show dramatic variations in RDW, MPV, NLR, and PLR, all markers of the ongoing inflammatory process, and these shifts can be tracked to keep a watchful eye on the disease's progression [14]. In SLE patients, PLR was also representative of the inflammatory response, disease activity, and tissue damage [15].

This study evaluated the PLR as possible predictor of EPO response in hemodialysis patients. we found statistically significant relations between EPO resistance and all of hemoglobin, hematocrit, RBCs and RDW (all were significantly higher among EPO low resistant patients). In agreement with our findings, **Hammed *et al.*** [16] found that EPO Responders had significantly higher Hb and hematocrit values, $P < 0.001$ in comparison with non-responders.

Also, we found that there was no statistically significant relation between EHRI and PLR values. In contrast to our findings, **Hammed *et al.*** [16] found that PLR was significantly higher in non-responders (151.17 ± 84.03 vs. 84.45 ± 26.66, $P < 0.001$). Additionally, **Taymez *et al.*** [17] found that PLR levels increased from the 25th to the 75th percentile on the EHRI ($P= 0.032$) when comparing the 25th and 50th percentiles. Moreover, **Sheikh *et al.*** [18] found that EPO resistant group had much higher mean values of platelet/lymphocyte ratio (PLR), with statistically significant difference as ($P=0.001$). This is mostly contributed to the difference in the study population characteristics regarding the ethnicity of patients, durations of their illness and different sample size, along with different ESA generics used in these studies.

In this study we demonstrated statistically significant positive linear correlations between PLR among studied patients and the MCH, MCHC and platelet count. While significant negative linear correlation was found between PLR among studied patients and ALC. Also, **El-Hafeez *et al.*** [19] revealed that patients' PLR was found to have a statistically significant (p 0.05) positive correlation with their Platelet count, and a statistically significant (p 0.05) negative correlation with their Hb and ALC. Additionally**, Ahmed *et al.*** [20] found that Positive correlations were found between PLR and MCH and PLR and ferritin in the patient group, while negative correlations were seen between PLR and Hb and PLR and ALC.

In this study we demonstrated that PLR was negatively correlated with all of serum creatinine, potassium, LDL cholesterol and TIBC, while PLR was significantly correlated with both serum sodium, creatinine clearance and serum ferritin. These findings reflecting association between PLR as a marker for the inflammation and the metabolic derangement in these population that comes in agreement with **El-Hafeez *et al.*** [19]**, Ahmed *et al.*** [20] **and Grilz *et al.*** [21]**.** Anemia and erythropoietin resistance are two complications of chronic kidney disease, and inflammation is a major risk factor for both. In addition, PLR is thought to be a measure for predicting anemia in hemodialysis patients because of its association with erythropoietin resistance [22].

In this research we found that PLR best cutoff value for predicting EPO resistance is ≥87.5 and area under curve was 0.517, with specificity, sensitivity, positive predictive value, and negative predictive value were 51.3%,56.1%, 52.6%, and 54.8% respectively with overall accuracy of 53.8% ($p>0.05$)

Based on the **Hammed *et al.*** [16] study, PLR <116.5 has 90% sensitivity and 70% specificity for prediction of EPO response with overall accuracy that was 82%, AUC = 0.79**.**

Sheikh *et al.* [18] found that PLR had a sensitivity of 93%, a specificity of 80%, a positive predictive

value of 82%, and a negative predictive value of 92%, yielding an overall accuracy of 87%, our cutoff value for PLR was 125.

Despite having a simple and readily available cheap biomarker of inflammation in CKD patients, we have certain limitations of our study being a cross-sectional single-center design not linking the causal outcome relationship and a relatively small number of included patients.

CONCLUSION

Despite being a simple marker of inflammation in many diseases, PLR did not appear to be useful in reflecting the EHRI in CKD patients. Thus, we recommend further future multicenter and nationwide study to stand on the suitable marker for EHRI in CKD population in Egypt.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Afsar B, Saglam M, Yuceturk C *et al.* (2013):** The relationship between red cell distribution width with erythropoietin resistance in iron replete hemodialysis patients. Eur J Intern Med., 24(3): 25-9.
2. **Smrzova J, Balla J, Bárány P (2005):** Inflammation, and resistance to erythropoiesis-stimulating agents--what do we know and what needs to be clarified? Nephrol Dial Transplant., 20: 2-7.
3. **López-Gómez J, Portolés J, Aljama P (2008):** Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int., 111: 75-81.
4. **Turkmen K, Guney I, Yerlikaya F *et al.* (2012):** The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. Ren Fail., 34(2):155-9.
5. **Valga F, Monzón T, Henriquez F *et al.* (2020):** Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios as markers of erythropoietin resistance in chronic haemodialysis patients: a multicentre cross-sectional study. Nefrologia, 40(3):320–7.
6. **Manuti J, Alwan A, Abd Ali M (2021):** Hyporesponsiviness to Erythropoietin Therapy in End Stage Renal Disease Patients on Regular Haemodialysis. Clinical Medicine Research, 10: 191-96.
7. **Esheba N, Mabrouk M, Elkhateeb M *et al.* (2021):** High Normal Thyrotropin (TSH) is Associated with Higher Needed Dose of Erythropoietin in Hemodialysis Patients. Journal of Advances in Medicine and Medical Research, 33: 49-55.
8. **Hung P, Yeh C, Hsiao C *et al.* (2021):** Erythropoietin use and the risk of stroke in patients on hemodialysis: A retrospective cohort study in Taiwan. Journal of the American Heart Association, 10: e019529. doi: 10.1161/JAHA.120.019529.
9. **Sato E, Sato S, Degawa M *et al.* (2022):** Effects of Zinc Acetate Hydrate Supplementation on Renal Anemia with Hypozincemia in Hemodialysis Patients. Toxins, 14: 746. doi: 10.3390/toxins14110746
10. **Wish J (2020):** Erythropoiesis-Stimulating Agent Hyporesponsiveness and Adverse Outcomes: Guilty as Charged?. Kidney Medicine, 2(5): 526–528.
11. **Benjamin S, Adam J, Krishna S *et al.* (2020):** Antibodies to Erythropoietin Are Associated with Erythropoietin Resistance in Hemodialysis Patients in KwaZulu-Natal (South Africa). Saudi Journal of Kidney Diseases and Transplantation, 31: 917-26.
12. **Embaby A, Hamed M, Ebian H *et al.* (2023)** Clinical utility of haematological inflammatory biomarkers in predicting 30-day mortality in hospitalised adult patients with COVID-19. Br J Haematol., 200(6):708-716.
13. **Hamed M, Hegazy A, Embaby A *et al.* (2022):** Identifying Independent Predictors of Mortality in COVID-19 Patients with Mucormycosis. Biomedical & Pharmacology Journal, 15(3): 1453-1467.
14. **Ali E, Embaby A, Ibrahim D (2022**) Mean Platelet Volume, Red Cell Distribution Width, And Lymphocyte Ratios As Surrogate Predictors Of Subclinical Inflammation In Schizophrenia: A Cross-Sectional Study. Euromediterranean Biomedical Journal, 17(39): 181-185.
15. **AbdElkader M, Nasr E, Fathy A *et al.* (2022):** The Relationship Between Lymphocyte and Both Neutrophil and Platelet Ratios In Systemic Lupus Erythematosus Activity. NeuroQuantology, 20: 8569-87.
16. **Hammed M, Tohammy M, Mohammed S *et al.* (2022):** Predictors of erythropoietin response in nondiabetic end-stage renal-disease patients on hemodialysis. Journal of Current Medical Research and Practice, 7: 310-15.
17. **Taymez D, Ucar E, Turkmen K *et al.* (2016):** The predictive value of platelet/lymphocyte ratio in hemodialysis patients with erythropoietin resistance. Therapeutic Apheresis and Dialysis, 20: 118-121.
18. **Sheikh E, Elwan N, Esheba N *et al.* (2021):** Assessment of platelet/lymphocyte ratio as a predictor of erythropoietin resistance in hemodialysis patients. Journal of Advances in Medicine and Medical Research, 33: 1-6.
19. **El-Hafeez A, Ahmed H, Al-Alashkar A *et al.* (2019):** Association between Neutrophil to Lymphocyte Ratio and Inflammatory Markers in Hemodialysis Patients. The Egyptian Journal of Hospital Medicine, 77: 5681-5689.
20. **Abd El-Hafeez H, Al-Ashkar A, Abo Mohamed N *et al.* (2020):** Association between neutrophil to lymphocyte ratio and inflammatory markers in hemodialysis patients. Al-Azhar Medical Journal, 49: 491-502.
21. **Grilz E, Posch F, Königsbrügge O *et al.* (2018):** Association of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio with the risk of thromboembolism and mortality in patients with cancer. Thrombosis and Haemostasis, 118: 1875-1884.
22. **Hamid D, Nienaa Y, Mostafa T (2022):** Alpha-lipoic acid improved anemia, erythropoietin resistance, maintained glycemic control, and reduced cardiovascular risk in diabetic patients on hemodialysis: a multi-center prospective randomized controlled study. Eur Rev Med Pharmac ol Sci., 26: 2313-232.