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Assessment of Platelet/ Lymphocyte Ratio as a Predictor of Erythropoietin Resistance in Hemodialysis Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author MNFA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors NESE and NME managed the analyses of the study. Author EHE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Platelet / lymphocyte ratio has recently been investigated in different clinical conditions associated with hemodialysis and its association with other diseases has been assessed. The purpose of the study was to assess platelet lymphocyte ratio as a predictor of erythropoietin resistance in hemodialysis patients.
Methods: The study population consisted of 60 hemodialysis patients, who were subdivided into two groups according to the response to erythropoietin stimulating agents (ESAs) .treatment. Group 1 included 30 patients treated with ESAs with good response to it and group 2 included 30 patients treated with ESAs but with resistance to it. The platelet/ lymphocyte ratio was calculated for each patient and compared between both groups.
Results: Platelet lymphocyte ratio of group 2 was significantly higher compared to that of group 1 (P=0.001).
Conclusion: PLR is a useful parameter to predict erythropoietin resistance in hemodialysis patients.

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Keywords: Platelet/ lymphocyte ratio; erythropoietin resistance; hemodialysis patients.

1. INTRODUCTION

Anemia is one of the common complications in patients with chronic kidney disease (CKD) and there is association between anemia and increased hospitalization and death risks in CKD patients [1]. The main cause of anemia in chronic kidney disease is decreased erythropoietin (EPO) production [2]. Therefore, treatment with erythropoietin using erythropoietin-stimulating agents (ESAs) in CKD patients has become the standard treatment for anemia in this patient's population [3].

The response to ESAs treatment in CKD patients is generally adequate, however a percentage of about 10 % not responding well to ESA, so-called ESA resistance [4]. EPO resistance is defined as the failure to achieve the target hemoglobin (Hb) concentration in patients who receive doses more than 300 IU/kg per week (20 000 IU/week) of erythropoietin or 1.5 mg/kg of darbepoetin alfa (100 mg/week), or who are in a continuous need for such high dosages to maintain the achieved target hemoglobin [5].

This resistance or decreased responsiveness is due to a variety of causes, which may be iron deficiency, blood loss, shortened life span of red blood cells (RBCs) and inflammation or infection, as the cytokines release in inflammatory state result in down-regulation of expression of erythropoietin receptors on erythrocyte precursors. In addition, there is increase in hepcidin production, which disrupts iron availability by diminishing intestinal iron absorption and release from reticuloendothelial cells [6].

Total Leukocyte count (TLC) can give a crude but sensitive assessment of inflammatory status, in a cheap and widely available manner. In hemodialysis (HD) patients, neutrophil/ lymphocyte ratio (NLR) was closely associated with increased inflammation [7]. However, recently the predictive value of platelet /lymphocyte ratio (PLR) for diagnosis of inflammation is considered to be better than that of NLR and PLR. kidney patients has begun to be used as a marker of some conditions as inflammation and damage of endothelium. More recently, it has also been used as a predictor of death in these patients [8].

The importance of PLR as a marker of death in patients with advanced kidney disease and patients on hemodialysis has been assessed and there was relationship between high PLR ratio and higher total and cardiovascular mortality rates in renal patients [9]. The PLR is related to erythropoietin resistance in patients with chronic kidney disease stage 5 who undergo hemodialysis [10-11].

Here, we assessed the platelet lymphocyte ratio as a predictor of erythropoietin resistance in hemodialysis patients.

2. PATIENTS AND METHODS

This prospective study was conducted on 60 patients, who had chronic kidney disease (CKD) stage 5 and were under hemodialysis (HD). They were enrolled from wards and dialysis units of Tanta University Hospital and El –Mahalla General hospital.

2.1 The Patients Were Divided into Two Groups

Group 1:30 patients on regular HD and receiving erythropoietin stimulating agent (ESA) with good response to it.

Group 2:30 patients on regular HD and receiving ESA but with ESA resistance.

2.2 Inclusion Criteria

Patients with CKD stage 5 on HD aged more than 18 years. Patients were on regular hemodialysis. They were treated by erythropoietin stimulating agents ESAs.

2.3 Exclusion Criteria

Patients with the following disorders were excluded from the study: iron deficiency, overt infection or inflammation, hospital admission within the preceding 3 months, history of blood transfusion in the last 3 months, hematological malignancy or patients receiving steroid treatment.

Full history, thorough physical examination and investigations: complete blood count (CBC), C-reactive protein, blood urea, serum creatinine, serum ferritin, serum iron, transferrin saturation, total iron binding capacity (TIBC), serum phosphorous, serum calcium, serum albumin, parathormone hormone. Platelet/lymphocyte ratio was calculated by dividing platelet count by lymphocyte count obtained from CBC.

2.4 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum). Significance of the obtained results was judged at the 5% level.

3. RESULTS

As shown in Table 1. group 2 had lower mean values of hemoglobin (Hb) concentration and absolute lymphocyte count than group 1 with statistical significant difference (*P*=0.001) for Hb concentration and (*P*=0.002) for absolute lymphocyte count. Group 2 had higher mean values of platelet/lymphocyte ratio (PLR), EHRI, and platelet count with statistical significant difference as (*P*=0.001) for PLR and EHRI, and (*P*=0.0025) for platelet count.

In group 1, PLR showed significant positive correlation with the following parameters: PTH (*P*=0.009) and serum phosphorus (*P*=0.004). EHRI, showed significant negative correlation with the following parameters: weight (*P*=-0.021) and Hb (*P*=-0.028) Table 2.

In group 2, PLR showed significant positive correlation with the following parameters: EHRI (*P*=0.001) and CRP (*P*=0.040). EHRI showed significant positive correlation with serum creatinine (*P*=0.009) and CRP (*P*=0.001). EHRI showed negative correlation with Kt/V (*P*=-0.020) Table 3.

4. DISCUSSION

As regard to CBC, this study found that hemoglobin Hb was significantly lower in group 2 who received higher doses of EPO than in group 1 who received lower doses of EPO, this was in an agreement with [12] who found that hemoglobin concentration was significantly lower in non–responders to rHuEPO treatment than in responders. Our results were also in an agreement with [13] who observed that the dose of EPO was inversely related to hemoglobin concentration and in agreement with [14] who observed significantly lower Hb concentration in patients with erythropoietin resistance than patients without erythropoietin resistance.

As regard platelet count, platelet count was significantly higher in group 2 than in group 1. This result could be due to the megakaryocyte stimulation that was reported in mice treated with high dose, short term EPO [15], this was in an agreement with [16] who found that patients who received higher EPO doses had higher platelet counts.

As regard lymphocyte count, in this study lymphocyte count was significantly lower in group 2 than in group 1. This could be explained by the fact that ESRD patients are immune deficient. This impairment of the immune system is aggravated by HD as it stimulates T cells and monocytes; but the introduction of EPO decreases the suppressor cell subpopulations and corrects the immunoglobulin synthesis. This result was in consistence with [17] who observed decreased lymphocyte count with usage of rHuEPO.

Platelet /lymphocyte ratio was significantly higher in group 2 who showed higher erythropoietin hyporesponsivness index EHRI, this was in an agreement with [18] who observed higher PLR in patients with higher EHRI. [14]

As regard erythropoietin hyporesponsivness index (EHRI), it was significantly higher in group 2 than in group 1, this was in an agreement with [19] who studied 677 hemodialysis patients and found that EHRI was significantly higher in EPO resistant group than in normo-responsive and hyper-responsive groups, and in an agreement with who studied 99 hemodialysis patients and observed higher EHRI in EPO resistant patients than in patients with good response to EPO treatment.

EHRI in group 1 showed significant negative correlation with Hb and body weight. But there was no correlation with the remaining studied parameters. This was in an agreement with [20] who studied parameters as age, gender, serum albumin and documented that those parameters were not determinant of EHRI. When we studied group 2 for the correlation of EHRI with the studied parameters, we found that serum calcium had no correlation with EHRI. Schneider et al. [21] as well declared that the concentrations of calcium did not associate with ESA resistance. The same result was recorded for serum ferritin, Lopez-Gomez et al. [13] as well found no significant correlation of serum ferritin concentration with EHRI. Also, serum iron, TIBC, Tsat showed non-significant negative correlation with EHRI. Gaweda et al. [22] also reported that higher Tsat values were associated with good EPO response.

Table 1. Comparison between the studied groups regarding some hematological parameters and erythropoietin hyporesponsiveness index (EHRI)

	Range		t. test	p. value
	Group 1	Group 2		
Hb (g/dl)	11–15	5.1–8.5	513.373	0.001*
PLT (×10^3/ µL of blood)	86-343	106–466	5.300	0.025*
Lymphocytes (×10^3/ µL of blood)	0.9–3.8	0.7–2.9	10.640	0.002*
PLR	37–144	100–291	43.021	0.001*
EHRI	8.28–14.8	36.8–60.7	788.200	0.001*

Hb: Hemoglobin. Plt: Platelet count. PLR: Platelet/lymphocyte ratio. EHRI: Erythropoietin hyporesponsiveness index

Table 2. Correlation of PLR and EHRI with other variables of group 1

Variable	PLR		EHRI	
	r	p	r	p
Age	0.029	0.877	-0.192	0.309
Weight	0.119	0.532	-0.421	0.021*
BMI	-0.149	0.432	-0.230	0.222
Hb	0.152	0.422	-0.402	0.028*
EHRI	-0.259	0.167		
PTH	0.467	0.009*	-0.227	0.229
Ferritin	-0.116	0.542	-0.220	0.242
Transferrin Saturation	-0.171	0.367	0.284	0.129
TIBC	0.148	0.434	-0.172	0.362
Serum Iron	0.028	0.885	0.031	0.871
Albumin	0.325	0.079	-0.194	0.305
Phosphorus	0.506	0.004*	-0.318	0.087
Calcium	0.173	0.361	-0.016	0.933
Creatinine	-0.213	0.258	0.113	0.551
Kt/V	-0.027	0.888	0.108	0.571
CRP	-0.333	0.072	0.269	0.150

BMI: Body mass index. Hb: Hemoglobin. EHRI: Erythropoietin hyporesponce index. PTH: Parathyroid hormone. TIBC: total iron binding capacity. Kt/V: Hemodialysis adequacy. CRP: C reactive protein

Table 3. Correlation of PLR and EHRI with other variables in group 2

With	PLT / Lymph		EHRI	
	r	p	r	p
Age	-0.254	0.175	-0.198	0.295
Weight	0.140	0.460	0.150	0.430
BMI	-0.015	0.937	-0.082	0.668
Hb	-0.047	0.806	-0.024	0.900
EHRI	0.725	0.001*		
PTH	0.048	0.800	0.264	0.159
Ferritin	0.049	0.799	-0.124	0.514
Transferrin Saturation	-0.025	0.897	-0.051	0.788
TIBC	0.001	0.994	-0.046	0.810
Serum Iron	0.001	0.996	-0.048	0.803
Albumin	-0.172	0.362	-0.134	0.479
Phosphorus	0.055	0.774	-0.169	0.372
Calcium	-0.222	0.238	-0.330	0.074
Creatinine	0.269	0.150	0.471	0.009*
Kt/V	0.221	0.242	-0.424	-0.020*
CRP	0.477	0.008*	0.577	0.001*

BMI: Body mass index. Hb: Hemoglobin. EHRI: Erythropoietin hyporesponsiveness index. PTH: Parathyroid hormone. TIBC: Total iron binding capacity. Kt/V: Hemodialysis adequacy. CRP: C reactive protein

Serum phosphorous as well correlated negatively with EHRI but without statistical significance. This result was opposite to that reported by [20] who documented that phosphate level positively correlated with EHRI. Serum albumin also showed non-significant negative correlation with EHRI. On the other hand, [23] declared that albumin is an important predictor EPO sensitivity.

As regard Kt/V as a measure of dialysis adequacy, this study demonstrated that EHRI negatively correlated with Kt/V in resistance patients with statistical significance, this was in an agreement to [20] who found that there was a negative relationship between resistance (EHRI) and Kt/V., and in contrast to [13] who declared that they could not find significant correlation of spKt/V with EHRI. As regard serum creatinine it positively correlated with EHRI, this was in an agreement with [21] who found that serum creatinine was strongly associated with EPO resistance in their study. CRP as well positively correlated with EHRI, this was in agreement with [14] who found that the ERI was positively associated with CRP.

EHRI was positively correlated to PLR, this was in an agreement with [18] who observed positive correlation between EHRI and PLR.

In group 1 patients, a statistically significant positive correlation of PTH and serum phosphorous with PLR was found, and non-statistically significant correlation of PLR with age, weight, Hb, TIBC, serum iron, serum albumin, and serum calcium was found. On the other hand, a non-statistically significant negative correlation of CRP, Kt/V, serum creatinine, Tsat, serum ferritin with EHRI was found.

In group 2 patients, a negative correlation with no statistical significance was found between PLR and age, BMI, Tsat, serum albumin, and serum calcium. PLR showed significant positive correlation with EHRI, this was in an agreement with [18] who observed positive correlation of EHRI with PLR. CRP showed positive statistically significant correlation with PLR, while Kt/V, serum creatinine serum phosphorous, serum iron, TIBC, serum ferritin, PTH, and BMI positively correlated with PLR with no statistical difference.

5. CONCLUSION

PLR was significantly higher in resistance group than in response group.

Positive correlation in resistance group between PLR and EHRI.

The sensitivity of PLR was 93% and the specificity was 80% and 82% for positive and 92% for negative predictive value with a predictive accuracy of 87% our cutoff value for PLR was 125.

Platelet / lymphocyte ratio can be used as a simple marker for predicting erythropoietin resistance in hemodialysis patients.

CONSENT

After selection of patients according to inclusion and exclusion criteria, all of them were subjected to the following after taking informed written consent

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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