Evaluation of Erythropoietin Stimulating Agent's Responsiveness and Associated Factors in Hemodialysis Patients with Anemia

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Abstract

Background: Chronic kidney disease (CKD) patients often develop erythropoietin-deficient anemia. Erythropoietin stimulating agents (ESAs) are the conventional treatment for CKD anemia, but patient responses vary. About 10%–15% of erythropoietin-treated patients may not respond, thus identifying hyporesponsiveness causes may help overcome resistance. **Objective:** This study is designed to evaluate ESA therapy's responsiveness and to identify possible contributing factors for ESA resistance. **Materials and Methods:** This observational cross-sectional study was conducted between September 2022 and February 2023 comprised 150 CKD and patients with anemia in a multicenter dialysis unit. Demographic, clinical, and laboratory data were obtained. The weekly body-weight-adjusted ESA dose divided by hemoglobin concentration is calculated as the erythropoietin resistance index (ERI). ERI values of 5 (responsive), 5–15 (hyporesponsive), and >15 (resistant). **Results:** A total of 150 patients were enrolled among whom 86 (57.3%) were males with a mean age 51.6 ± 14.9 years. Regarding responses of the patients to ESA, 81 patients (54%) were hyporesponsive, 66 patients (44%) were resistanct and 3 patients (2%) were responsive. There was a significant difference in response according to age, body mass index (BMI), and the presence of co-existing diseases among study groups. Phosphate level was directly associated with the presence of resistance. ERI was positively correlated with dialysis frequency, ESA dose, serum iron, and transferrin saturation. **Conclusion:** According to the findings of this study, many factors can influence response levels in patients with CKD undergoing hemodialysis based on ERI (age, BMI, presence of co-existing diseases, serum phosphorus, serum iron, and transferrin saturation).

Keywords: Anemia, erythropoietin resistance index (ERI), ESA, hemodialysis, hemoglobin

Introduction

Chronic kidney disease (CKD) involves long-term renal impairment or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for 3 months. The kidney disease improving global outcome (KDIGO) 2012 guideline suggested six GFR and three albuminuria categories.[1] End stage renal disease (ESRD), which is the result of CKD progressing, is defined as "loss of kidney function such that life is not sustainably possible in the absence of renal replacement therapy." In 2015, the US Renal Data System (USRDS) reported 124,411 new ESRD diagnoses and the disease has spread by 20,000 cases annually.[2,3]

Except for the Sulaymaniyah and Erbil provinces, all studies in Iraq have found that the proportion of male patients with ESRD is higher than the proportion of female patients.[4,5] Diabetes is the most common cause of ESRD, with hypertension coming in second. Volume overload, hypertension, anemia, and metabolic abnormalities are also indications of ESRD.[2]

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Renal replacement therapy, including hemodialysis and peritoneal dialysis, is the primary life-saving treatment for ESRD patients.[6] Also, considered the most widespread initial form of dialysis, followed by peritoneal dialysis and according to USRDS, approximately 400,000 patients in the US are maintained on hemodialysis.[7,8] Conservative management (CM) may help renal function, symptoms, acidosis, anemia, bone and mineral metabolism, blood pressure, and nutrition.[9]

According to the World Health Organization's Global Anemia Report 2011, there were 273.2 million instances of anemia. The developing world has the highest frequency of anemia.[10]

CKD is a major risk factor for anemia and is characterized as normocytic, normochromic, and hypo-proliferative, though microcytic or macrocytic anemia may be present in some cases.[11] Erythropoietin (EPO) synthesis and iron deficiency are key causes of CKD anemia.[12]

Erythropoietin stimulating agents (ESAs) are the standard treatment for CKD anemia and improve outcomes. ESA treatment helps dialysis patients maintain hemoglobin levels of 11–12 g/dL. The food and drug administration (FDA) approved the first ESA, epoetin alfa, in 1989. The recommended beginning dose is 50–100 IU/kg subcutaneously, one to three times per week, to increase hemoglobin by 0.3 g/dL/week.[13,14]

Before initiating ESA therapy, iron deficiency must be evaluated. Iron replacement can be administered orally or intravenously, though the oral route is less efficacious in hemodialysis patients.[13] Approximately 10%–15% of individuals receiving erythropoietin therapy may be less receptive to the treatment.[15] Several factors have been linked to ESA hyporesponsiveness, including iron deficiency, secondary hyperparathyroidism, insufficient dialysis, inflammation, malnutrition, the use of drugs such as Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs), and the presence of neutralizing antibodies to ESAs.[16]

The current work was designed to evaluate ESA therapy's responsiveness and to identify possible contributing factors for ESA resistance.

Materials and Methods

This cross-sectional study had been carried out in three Iraqi dialysis centers; the dialysis unit in Al-Emamian Al-Kadumian Medical City, AL-Karama Teaching Hospital, and Balad General Hospital by using the GAMPRO AK98 and Fresenius dialysis system. 150 hemodialysis patients with ESRD and anemia were studied after 12 weeks of ESA therapy.

The inclusion criteria were patients over 18 with baseline hemoglobin (HB) levels less than 11 gm/dL and on regular HD who received ESA (Eprex) for 12 weeks and had 3–4-h hemodialysis sessions (1–3) per week.

Patients who did not get treatment regularly and had a history of blood loss, active bleeding, active hemolysis, blood transfusion during ESA treatment, kidney transplant, polycystic disease, hematologic condition, or cancer were excluded.

Age, gender, smoking history, length and frequency of dialysis, ESA dose (IU/week), body mass index (BMI), iron type and dosage, comorbidities like coronary artery disease, chronic heart failure, diabetes mellitus, and hypertension, other medications like ACE, ARB, and statins, and dialyzer type (high flux or low flux) were collected by using a specific datasheet.

After 3 months of treatment, blood samples were collected predialysis and before heparin, and the first collection date that relates to the HB baseline was collected from the patient file. ERI was computed by dividing the weekly weight-adjusted EPO dose (IU/kg/week) by the hemoglobin level (g/dL) over 3 months.[14,15] ERI values characterized individuals as ERI (responsive) < 5, ERI (hyporesponsive) = 5–15, or ERI (resistant) >15.[17]

Statistical analysis

The data were statistically analyzed by using Excel and R (version 4.2.2). As statistical tests, mean, standard deviation, median with range, percentage, χ^2 test with Yates' correction or Fisher's exact test, ANOVA test (one-way), Kruskal–Walli's rank-sum tests, post hoc test, Pearson's product-moment, and Spearman's rank correlation coefficient were used. Statistical significance was determined as a *P*-value of less than or equal to 0.05.

Ethical approval

Written consent was obtained from all patients after explaining the study protocol in detail. The study protocol and the subject information and the consent form were reviewed and approved by the Research Ethics Committee according to Approval No. 13 on May 23, 2023, by the College of Pharmacy, University of Al-Mustansiriyah.

Results

Regarding responses of the patients to ESA, 81 patients (54%) were hyporesponsive, 66 patients (44%) were resistance, and 3 patients (2%) were responsive as shown in Table 1.

The mean age of all participants was 51.6 ± 14.9, with significantly different (*P*-value = 0.009) among the three groups, especially between hyporesponse and resistance. Lower BMI patients had increased ERI ($P \leq 0.001$). Additionally, there was significant difference among study groups according to the number of co-existing diseases ($P = 0.002$) as shown in Table 2.

Table 1: Patient responsiveness to ESA according to ERI

Characteristics	Response, *N* = 3*	Hyporesponse, *N*= 81*	Resistance, *N* = 66*	*P*-value **
HB after dialysis	12.1 ± 1.0	10.0 ± 1.3	8.9 ± 1.4	<0.001
Weight-adjusted dose	52.9 ± 2.1	104.9 ± 26.0	192.4 ± 55.0	<0.001
ERI	4.4 ± 0.3	10.5 ± 2.6	22.2 ± 8.3	<0.001

* Data are expressed as Mean ± SD

** One-way ANOVA, post hoc test, $P < 0.$ 0.001: highly significant

ERI: erythropoietin resistance index, ESA: erythropoietin stimulating agent

Table 2: Baseline demographics of the subjects in three groups divided by ERI

Characteristics	Overall, *N* = 150*	Response, *N* = 3*	Hyporesponse, *N* = 811	Resistance, *N* = 66*	*P*-value**
Age, years	51.6 ± 14.9	52.3 ± 9.8	55.0 ± 14.1	47.4 ± 15.3	0.009
≥50 years	88 (58.6%)	2 (2.3%)	58 (65.9%)	28 (31.8%)	<0.001
18–50 years	62 (41.4%)	1 (1.6%)	23 (37.1%)	38 (61.3%)	
Sex					
Males	86 (57.3%)	3 (3.5%)	49 (57.0%)	34 (39.5%)	0.2
Females	64 (42.7%)	0 (0.0%)	32 (50.0%)	32 (50.0%)	
BMI, kg/m^2	26.0 ± 5.7	22.0 ± 5.0	27.8 ± 5.6	24.1 ± 5.3	<0.001
>24.9	79 (52.7%)	1 (1.3%)	53 (67.1%)	25 (31.6%)	<0.001
18.5–24.9	64 (42.1%)	1 (1.6%)	28 (43.8%)	35 (54.7%)	
<18.5	7 (4.3%)	1 (14.3%)	0 (0.0%)	6 (85.7%)	
Co-exiting disease (No.)	1.5 ± 0.8	2.0 ± 0.0	1.7 ± 0.8	1.2 ± 0.8	0.002
Yes	135 (90.0%)	3 (2.2%)	76 (56.3%)	56 (41.5%)	0.2
No	15 (10.0%)	0 (0.0%)	5 (33.3%)	10 (66.7%)	
Drug use					
Yes	101 (67.3%)	2 (2.0%)	57 (56.4%)	42 (41.6%)	0.8
No	49(32.7%)	1 (2.0%)	24 (49.0%)	24 (49.0%)	
Type of dialyzer					
Low flux	82 (54.6%)	2 (2.4%)	46 (56.1%)	34 (41.5%)	0.8
High flux	68 (45.4%)	1 (1.5%)	35 (51.5%)	32 (47.1%)	
Smoking status					
Nonsmoker	132 (88.0%)	3 (2.3%)	72 (54.5%)	57 (43.2%)	0.9
Smoker	18 (12.0%)	0 (0.0%)	9 (50.0%)	9 (50.0%)	
Duration of dialysis	36.6 ± 27.7	13.7 ± 11.7	36.8 ± 28.3	37.4 ± 27.3	0.3
≥24 (months)	103 (68.7%)	1 (1.0%)	55 (53.4%)	47 (45.6%)	0.3
<24 (months)	47 (31.3%)	2 (4.3%)	26 (55.3%)	19 (40.4%)	
Frequency of dialysis times/week	2.6 ± 0.5	3.0 ± 0.0	2.6 ± 0.5	2.7 ± 0.5	0.071
3	96 (64.0%)	3 (3.1%)	46 (47.9%)	47 (49.0%)	0.14
2	53 (35.3%)	0 (0.0%)	34 (64.2%)	19 (35.8%)	
1	1 (00.7%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	

* Data are expressed as Mean ± SD; *n* (%)

**One-way ANOVA; Pearson's Chi-squared test; Fisher's exact test; post hoc test, $P < 0.05$: significant, $P < 0.$ 0.001: highly significant, $P > 0.05$: not significant

According to the results, phosphate level was directly associated with the presence of resistance ($P = 0.027$) as shown in Table 3. Furthermore, after 3 months of therapy, resistance patients had a significantly lower HB level ($P < 0.001$). Also, the median hemoglobin change was highly significant ($P < 0.001$). No significant difference in serum intact parathyroid hormone (PTH), total calcium (Ca), phosphorus (PO4), total iron binding capacity (TIBC), transferrin saturation (TSA), ferritin, and hemoglobin (Hb) at baseline.

Erythropoietin resistance Index correlated negatively with age and BMI, but positively with dialysis frequency. Additionally, ERI was positively correlated with ESA dosage, serum iron, and transferrin saturation. In contrast, ERI was inversely linked with hemoglobin concentration ($P < 0.0001$) as demonstrated in Table 4.

Discussion

The ERI examined ESA response in stable chronic HD patients. Hence, the ERI was directly proportional to

Table 3: Biochemical assessment of the study groups

Characteristics	Response, *N* = 3*	Hyporesponse, *N* = 81*	Resistance, *N* = 66*	*P*-value**
Calcium	8.6 ± 1.3	8.8 ± 1.2	8.7 ± 1.2	>0.9
Phosphorus	2.9 ± 0.8	5.1 ± 1.4	5.3 ± 1.7	0.027
Parathyroid hormone	202.0 (183.0–212.0)	250.0 (113.0–372.0)	204.0 (111.2–402.8)	>0.9
Serum iron	32.5 ± 19.8	54.3 ± 24.8	62.7 ± 33.1	0.069
TIBC	319.9 ± 154.8	296.7 ± 81.7	326.6 ± 92.7	0.12
TSA	16.3 ± 0.8	19.2 ± 8.8	21.3 ± 14.6	0.5
Ferritin	749.7 ± 412.9	722.8 ± 372.8	664.0 ± 343.4	0.6
Hb at baseline	9.6 ± 0.2	9.5 ± 0.8	9.1 ± 1.1	0.071
Hb post 3 months of dialysis	11.5 ± 1.0	10.0 ± 1.3	8.9 ± 1.4	<0.001
Hb change	2.4 (2.0–3.1)	0.6 (−0.4 to 1.5)	−0.4 (−0.9 to 0.5)	<0.001

TIBC: total iron binding capacity, TSA: transferrin saturation, Hb: hemoglobin

* Data are expressed as Mean ± SD; median (IQR)

** One-way ANOVA, Kruskal–Walli's rank-sum test; post hoc test, $P < 0.05$: significant, $P < 0.001$: highly significant, $P > 0.05$: not significant

Table 4: Correlation between ERI and different parameters of the study groups

Characteristics	ERI*	*P*-value**
Age, years	−0.25	0.001
BMI	−0.31	<0.001
Duration of dialysis	0.09	0.25
Frequency of dialysis/week	0.18	0.025
Dose of Eprex IU/week	0.67	<0.0001
Dose of iron (mg)	0.14	0.19
Serum iron	0.29	0.0003
TIBC	−0.11	0.16
TSA	0.22	0.005
Ferritin	−0.01	0.83
Serum Ca	−0.05	0.52
Serum PO4	0.09	0.23
PTH	0.04	0.57
Hb predialysis	−0.35	<0.0001
Hb postdialysis	−0.52	<0.0001
Hb change	−0.29	<0.0001

ERI: erythropoietin resistance index, BMI: body mass index, TIBC: total iron binding capacity, TSA: transferrin saturation, PTH: parathyroid hormone, Hb: hemoglobin

*Correlation coefficient

**Pearson's product-moment correlation; Spearman's rank correlation

weight-adjusted dosage and inversely proportional to HB, matching Chait *et al*.[18]

The resistant group was much more younger than the responder group. Petrulienė's[19] study found that ERI resistance group HD patients were younger than ERI response group HD patients. Age had no effect on response,[11,20] resistance occurred in younger patients possibly due to inflammation, iron deficiency, malnutrition, inadequate dialysis, and hyperparathyroidism.[15]

The current study showed that the resistance and hyporesponse groups contained more participants than the response group, hence their BMIs differed significantly and patients with lower BMI had higher ERI. Malnutrition induces IL-6 and TNF-α-induced inflammation, arteriosclerosis, and EPO resistance.[17] Kalantar-Zadeh *et al*.[21] found a positive correlation between malnutrition scores and ERI, whereas Samavat[20] found low BMI caused erythropoietin resistance.

Furthermore, the hyporesponse group was significantly different from the resistance group according to the number of co-existing diseases. One possibility could be that patients in the hyporesponse group were older than those in the resistance group which may explain the increased number of co-existing diseased, as demonstrated by Franceschi *et al*.[22] The result of the current study conflicts with those made by López-Gómez *et al*.,[17] who reported that patients with severe anemia demonstrate greater EPO resistance, which is most likely related to comorbidities. However, the same study found that not all comorbidity factors have the same influence on erythropoietin response. Antecedents of heart disease were not linked to ERI, whereas other factors had a negative effect on ERI. In addition, there were no significant differences in ERI between patients with and without hypertension.[17] Petrulienė *et al*.[19] reported in 2017, "During the evaluation of concurrent diseases, it is found that there were statistically significantly fewer patients with diabetes mellitus (DM) in the resistant group than in the group of patients who responded well to ESA."

The current study found higher phosphorus levels in the ESA resistance group than in the response group. Manuti *et al*.[11] and Samavat *et al*.[20] found that Hb levels were negatively associated with serum phosphorus and that ESA resistance was directly related to phosphate levels. Due to the increasing loss of functional nephrons in hemodialysis patients, phosphate homeostasis is lost, which causes persistent hyperphosphatemia. By increasing serum PO4, hyperphosphatemia produces secondary hyperparathyroidism, and hyperparathyroidism results in bone marrow fibrosis and ESA resistance.[20,23]

Additionally, the correlation between ERI and different parameters of the study groups revealed that age was negatively correlated with ERI (P value = 0.001). In Petruliené's[19] study, it was demonstrated that the ERI increases as age decreases. Also, the correlation between BMI and ERI was negative as shown by López-Gómez *et al*.[17] found an inverse correlation between BMI and ERI values. Our results showed that dialysis frequency was positively correlated with ERI. Patients who receive dialysis 3 times per week but have shorter HD sessions and do not respond well to treatment.[24]

Iron deficiency in HD patients promotes ESA resistance,[16] which contradicts our findings. We discovered no correlation between serum ferritin and ERI, which matches Samavat *et al*.[20] Serum ferritin, an acute phase reactant, is raised in systemic inflammation, including CKD.[25] In contrast, serum iron, TSA, and ERI were positively associated. Several studies found a negative correlation between TSA and ERI.[17,19] Some HD patients develop anemia even with IV iron, indicating that other factors are involved.[12] Ferritin and TSA are affected by inflammation, which may lower their ESA resistance prediction capacity.[19] Since these data were collected from three hemodialysis centers in Iraq, it's not clear if the results can be generalized to all HD patients. To confirm these results and determine whether or not they apply to other HD populations, further research with substantial sample sizes and countrywide is required.

Conclusions

According to the findings of this study, many factors can influence response levels in patients with CKD undergoing hemodialysis based on ERI (age, BMI, number of diseases, serum phosphorus, serum iron, and transferrin saturation). In clinical practice, routinely analyzed data can be employed to stratify patients based on their risk of ESA resistance, which may aid in the assignment of suitable treatment methods.

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Conflicts of interest

There is no conflict of interest.

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