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Predicting Resistance to Recombinant Human Erythropoietin Therapy in CKD Patients on Maintenance Hemodialysis

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Abstract: ***Background:*** ***Anemia is a common complication associated with chronic kidney disease (CKD), and optimal treatment requires appropriate diagnosis, recombinant human erythropoietin (rHuEPO) and iron therapy, and close monitoring of response. Approximately 5-10% of these patients receiving rHuEPO therapy; however, appear to be hypo-responsive to this drug. This study aimed to identifysome determinants of rHuEPO hypo-responsiveness in anemic CKD patients on maintenance hemodialysis.*** ***Method:*** ***Seventy patients with CKD on maintenance hemodialysis receiving rHuEPO and (20) control subjects were enrolled in this case-control prospective study.Erythropoietin resistance index (ERI), calculated as the weekly weight-adjusted dose of rHuEPO divided by the hemoglobin level was determined to evaluate the dose–response effect of rHuEPO therapy. Determinants of rHuEPO hypo-responsiveness were identified by univariate logistic regression analyses.*** ***Results:*** ***Approximately half of patients were inadequately responded to rHuEPO therapywith an ERI value >0.0365 µg/kg/week/g hemoglobin. Univariate analyses revealed that duration of dialysis (years), BMI and serum albumin were the most important determinants of rHuEPO hypo-responsiveness and an inverse relationship had been found between these determinants and ERI.*** ***Conclusion:*** ***easily available clinical parameters and routine laboratory parameters can predict hypo-responsiveness to rHuEPO therapy in hemodialysis patients.***

Keywords: CKD, Anemia, rHuEPO hypo-responsiveness, ERI

1. Introduction

Chronic kidney disease (CKD) is common and continues to rise globally. It is a risk factor for end stage renal disease (ESRD) and is also a strong risk factor for cardiovascular disease (CVD) as well as mortality[1]. ESRD patients require regular courses of dialysis or kidney transplantation, and dialysis is only temporary that does not replace all of the renal functions[2].

Anemia is defined as a reduction in one or more of the main red blood cell (RBC) measurements, hemoglobin level, hematocrit, or red blood cell count. The World Health Organization (WHO) defines anemia as a hemoglobin concentration < 13 g/dl in men and post-menopausal women, and < 12 g/dl in pre-menopausal women[3].

According to the National Kidney Foundation Kidney-Disease Outcomes Quality Initiative (NKF-KDOQI), anemia can be defined as hemoglobin concentrations of less than 13.5g/dl for men and less than 12.0g/dl for women[4]. Regardless of the definition, anemia is a common complication of CKD which develops early in the course of the disease with increasing its frequency with the reduction in renal function[5] and is typically normocytic, normochromic, and hypoproliferative[6].

Optimal treatment of anemia due to CKD requires appropriate diagnosis, erythropoietin (EPO) and iron therapy, and close monitoring of response[7]. This intervention has replaced transfusions as the corner stone of treatment and improved the survival of CKD anemic patients[3].

Methoxy polyethylene glycol-epoetin beta (MPGE-β) is a chemically synthesized recombinant human erythropoietin (rHuEPO) with a much longer half-life than EPO which enables it to be administered or injected in a once monthly dosing regimen[8]. It can be produced by recombinant DNA technology in Chinese hamster ovary cells[9]. Like endogenous EPO, rHuEPO stimulates the proliferation and differentiation of erythroid progenitor cells in bone marrow[10].

Although the majority of CKD patients respond adequately to rHuEPOs, 10-20% of these patients develop resistance to this therapy[11]. For the NKF-KDOQI guidelines, hypo-responsiveness to rHuEPOs therapy is defined by, at least, one of these conditions:

A significant increase in the rHuEPO dose required to maintain a certain hemoglobin level, a significant decrease in hemoglobin level at a constant rHuEPO dose, or a failure to increase the hemoglobin level to higher values than 11 g/dl, despite the administration of a rHuEPO dose equivalent to epoetin higher than 500 IU/kg/week[12].

The erythropoietin resistance index (ERI) which defined as the weekly weight-adjusted rHuEPO dose (U or µg/kg/week) divided by hemoglobin level (g/dl), is an alternative method, that considered by some authors, as a better way to measure the degree of rHuEPOs resistance. An ERI value >0.02 µg/kg/week/g hemoglobin or >4.19 U/kg/week/g hemoglobin indicates resistance to rHuEPOs. This ERI index was calculated population-based in a cross-sectional fashion at baseline[13].

Hypo-responsiveness to rHuEPOs therapy can have many underlying causes, and the most common causes involve iron deficiency (absolute or functional), and inflammation[5]. Other possible risk factors for developing rHuEPO hypo-responsiveness involve genetic polymorphism, hyperparathyroidism, inadequate dialysis, chronic blood loss, aluminum overload, nutrient deficiencies, and non-compliance to rHuEPO therapy[14].Hence, this study is designed to identify some determinantsofrHuEPO hypo-responsiveness in CKD patients on maintenance hemodialysis.

2. Materials and Methods

This case-control prospective study was carried out at Medical City Complex, Baghdad Teaching Hospital, Iraqi center of kidney dialysis under the supervision of consultant nephrologist from November 2015 until June 2016. Only (90) subjects completed the courses of the study successfully. These subjects were recruited into the following groups:

Group (A): Includes 70 patients with CKD receiving rHuEPO (methoxy polyethylene glycol epoetin beta (MIRCERA®) pre-filled syringe containing 50, 100 or 200 µg in 0.3 ml supplied by Roche Diagnostics GmbH, Mannheim, Germany). The dose was individualized to achieve and maintain hemoglobin levels between 10-12 g/dl.

Group (B): Includes 20 healthy subjects without medical illnesses such as diabetes mellitus, hypertension, or renal disease including current or prior history of renal stone.
The study protocol was approved by the local ethics committee in college of pharmacy, Baghdad University, Iraq but without specific informed consent from patients.

Inclusion and exclusion criteria
The primary inclusion criteria involved patients with chronic renal failure on maintenance hemodialysis for at least six months. Secondary inclusion criteria involved patients without functional iron deficiency (which is defined on the basis of transferrin saturation (TSAT)<20% and serum ferritin <100 ng/ml). Exclusion criteria involve the following: acute renal failure, age <18 years, inadequate data, hypertensive crises (diastolic blood pressure > 120mm Hg), psychiatric disorders and CNS diseases, renal carcinoma, and recent symptoms and signs of bleeding that required blood transfusion.

Blood sampling
Five milliliters of venous blood sample were drawn from each patient in the morning at 6:00 AM – 8:00 AM just prior to the start of the dialysis session after an overnight fasting from hemodialysis needle puncture site 48–72 hours after last dialysis. Sample were drawn from each patient at the beginning of the study (as baseline sample), then after 3 months and after 6 months of baseline sample to follow-up the changes in the studied parameters. During this time all the patients continued to receive MPGE-β. Blood sample was transferred into clean gel tube (that contains clot activator), left at room temperature for at least 30 minutes for clotting, centrifuged for 5 – 10 minutes at 3000 rpm to obtain serum. Serum then was stored at (–40ºC) until time for the assay. Single blood sample was drawn from each subject of the control group.

Evaluation of Patients' Response to rHuEPO
According to hemoglobin level changes (elevation exceeded 30% of baseline value or did not exceed 15% of baseline value for 3 consecutive months) and whether or not there was an achievement of target hemoglobin level (between 10-12 g/dl); all patients were divided into good-responsive and hypo-responsive groups[15].

Determination of Erythropoietin Resistance Index
In order to take into account both rHuEPO dose and hemoglobin levels (thus providing a more reliable indication of responsiveness to rHuEPO treatment); erythropoietin resistance index is calculated for each patient only at the end of the study as follows[16]:

$$ERI = \frac{\text{rHuEPO (µg/kg/week)}}{\text{Hemoglobin (g/dl)}}$$

ERI is calculated in µg/kg/week/g/dl and by using a formula that equates the protein mass of the two molecules (200 IU rHuEPO = 1 µg darbepoetin-alfa), ERI can be converted to U/kg/week/g/dl by multiplying with 200[17]. By means of the ERI values, patients were further divided into quartiles.

Statistical Analysis
Statistical calculations were performed using the SPSSprogram (version 20.0) (SPSS Inc., Chicago, Illinois, USA) and Minitab version 17 software. In all comparisons, a p value <0.05 was considered statistically significant. Anderson Darling test was performed to test the adherence of continuous variables to normal distribution. Normally distributed variables presented using their mean and standard deviation and parametric tests were used, while non-normally distributed variables described by their median and their interquartile range (IQR) and non-parametric tests were used. Discrete variables presented using their number and percentages. The chi-square test was used for comparisons of discrete variables between each study group.Binary logistics regression analysis was used to assess the predictors of anemic resistance (via ERI above Q4), and the relative risk (RR) and its 95% confidence interval (CI) were used to examine this relationship.

3. Results

Demographic data of the study groups are expressed in table 1, andcharacterization of CKD patients group is summarized in table 2. The subjects enrolled in the present study were matched. However, clinically there was significant ($p<0.05$) elevation in serum urea, creatinine, uric acid, glucose, and total protein in patients group as compared to control group. Medications history was positive as the majority of these patients were taking folic acid, multi-vitamins, calcium carbonate or sevelamer, alfa-calcidol and some of them were treating with antihypertensive agents and some of them were receiving antidiabetic drugs.

Table 1: Demographic data of the study groups

		Control (n=20)		Patient (n=70)		P value
		Mean	*SD*	*Mean*	*SD*	
Age (years)		46.2	6.3	49.3	7.4	0.071[a]
Weight (kg)		72.35	13.66	75.4	17.11	0.466 [a]
Height (m)		1.695	0.085	1.681	0.076	0.484 [a]
BMI (kg/m^2)		25.45	4.95	27.72	5.17	0.331 [a]
Pulse rate (bpm)		77.95	9.91	77.05	13.02	0.777 [a]
Mean Pressure(mmHg)		101.84	7.65	103.13	12.76	0.667 [a]
Urea (mg/dl)		31.56	7.41	121.61	43.55	<0.001 [a]
Creatinine (mg/dl)		0.85	0.29	6.04	1.76	<0.001[a]
Uric acid (mg/dl)		5.73	0.87	6.92	2.06	0.0003[a]
Glucose (mg/dl)		88.21	11.97	98.51	24.98	0.012[a]
Total protein(g/dl)		7.08	0.71	5.68	1.27	<0.001 [a]
		(n)	%	(n)	%	
Gender	*Male*	10	50	40	57.1	0.571[b]
	Female	10	50	30	42.9	
Consanguinity	*No*	15	75	49	70	0.663 [b]
	Yes	5	25	21	30	

[a] : *Independent 2 sample t-test*
[b] : *Chi square test*
SD : Standard Deviation

Table 2: Disease characteristics of patients (n=70).

Variables		*(n)*	*(%)*
Ex-Smoker		24	34.3
Ex-Alcoholic		24	34.3
Causes of CKD	*Unknown*	27	38.6
	Diabetes Mellitus	20	28.6
	Hypertension	6	8.6
	renal stone	5	7.1
	PCKD	6	8.6
	Congenital	3	4.3
	Others[*]	3	4.3
Family history (Yes)		17	24.3
Hepatitis C (Yes)		36	51.4
Chronic illnesses	*Hypertension*	64	91.4
	Diabetes Mellitus	21	30
	Angina	5	7.1
	Stroke	4	5.7
	CHF	1	1.4
		Median	*IQR*
Duration of dialysis (years)		2	1 – 5

[*] : *Cancer, Glomerulonephritis, and SLE each one presents in one case*
CHF: Congestive Heart Failure
PCKD: Poly Cystic Kidney Disease

Hemoglobin Level at Baseline

Results presented in table 3 showed that patients group had significantly lower ($p<0.05$) hemoglobin level as compared to control group.

rHuEPO Dose Adjustment

During this study the dose of rHuEPO received by patients was adjusted according to hemoglobin response and as shown in table 4, the dose was increased significantly ($p<0.05$) from baseline toward 3 months (mean difference of dose elevation was 0.36), while this elevation was non-significant from 3 to 6 months.

Hemoglobin Level after Dose Adjustment

Results presented in table 5 showed that hemoglobin level in patients group did not differ significantly through-out the study.

Table 3: Hemoglobin level (g/dl) in study groups at baseline.

Control		Patients		P value
Mean	*SD*	*Mean*	*SD*	
14.26	1.18	8.23	1.41	<0.001
Independent 2 sample t-test				

Table 4: Dose of rHuEPO (µg/kg/week) received by patients through-out the study.

	Mean	SD	Minimum	Maximum	P value	Difference (95% CI)
baseline	1.235	0.57	0.48	2.78	--	--
3 months	1.594	0.58	0.52	2.78	<0.001	0.358 (0.263 - 0.453)
6 months	1.606	0.64	0.52	3.00	0.667	0.012 (0.046 - 0.072)
Paired t-test used to calculate p value between two consecutive 3 months						

Table 5: Hemoglobin levels (g/dl) in patients group through-out the study. Data expressed as mean ± SD.

Baseline	3 months	6 months	P value
8.23 ± 1.41	8.78 ± 1.55	8.41 ± 1.53	0.089
One way ANOVA (parametric test)			

Response to rHuEPO Therapy

Approximately about half of patients in this study were adequately responded to rHuEPO therapy that increased and maintained a stable hemoglobinconcentrations through-out the study while approximately the other half were inadequately responded to therapy as illustrated in table 6.

Relationship between ERI and Response to rHuEPO Therapy

It had been found that ERI was significantly lower in good response than the hypo-response group to rHuEPO therapy as shown in table 7.

Table 6: Rate of response to rHuEPO therapy in patients

	Number	Percentage
Good response	36	51.4
Hypo response	34	48.6

Table 7: ERI (µg/kg/week/g) of patients divided by response to rHuEPO therapy.

Good response		Hypo-response		P value
Median	*IQR*	*Median*	*IQR*	
0.03	0.02275 – 0.04725	0.0605	0.041 – 0.077	<0.001
Mann Whitney U test				

Receiver Operator Curve (ROC) Analysis of ERI Validity for Predicting rHuEPO Response to Treatment

ROC analysis was performed to test whether ERI was a good differentiator between good- and hypo-response patients. As illustrated in tables 8 and 9 and in figure 1, ERI in this study had good ability to predict whether patients will have good response to rHuEPO therapy or not at value of less than or equal to (0.0365 µg/kg/week/g) with 91.7% specificity that patient is good responder to rHuEPO therapy.

Table 8: Receiver operator curve (ROC) of ERI to predict patient's response to rHuEPO therapy.

AUC	95%CI of AUC	P value
0.820	0.720 – 0.920	<0.001
AUC : area under the curve *CI: confidence interval*		

Table 9: Validity of ERI in predicting patient response to rHuEPO therapy by using ROC analysis.

Cut-off	Sensitivity	Specificity	Accuracy	PPV at pretest probability		NPV at pretest probability
				50%	90%	10%
≤0.0365	67.6%	91.7%	79.3%	89.1%	98.65%	96.2%
Values less than the cut-off indicate good respond to rHuEPO therapy *PPV : positive predictive value* *NPV : negative predictive value*						

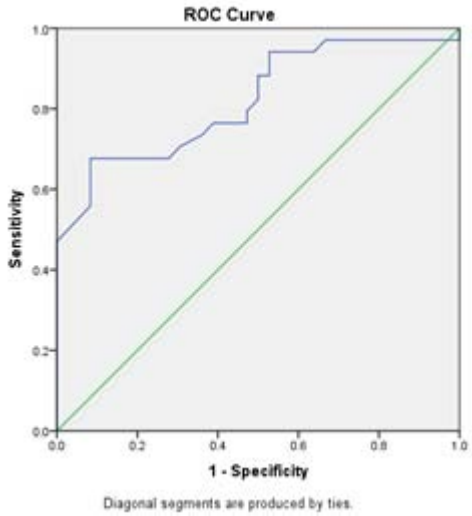

Figure 1: ROC analysis of ERI to predict patient's response to rHuEPO therapy.

Determinants of rHuEPO Resistance from Clinical Characteristic, Laboratory and Dialysis Efficacy Parameters

Results expressed in table 10 showed a classification of patients group according to their ERI into four quartiles. The cut-off values were Quartile 1 < 0.03, Quartile 2 (0.03 – 0.0435), Quartile 3 (0.0436 – 0.0713) and Quartile 4 > 0.0713 respectively. Patients in the upper quartile were defined as hypo-responders.

Results presented in table 11 showed univariate analyses of different determinants for rHuEPO resistance in quartile 4 patients only. Univariate analyses revealed that duration of dialysis (in years), BMI and serum albumin were the most important determinants of rHuEPO resistance and an inverse relationship had been found between these determinants and ERI. Therefore, as duration of dialysis increase there is a reduction in the risk of rHuEPO resistance (dialysis improves resistance), low BMI has higher ERI, as well as an inverse relationship between serum albumin and ERI has been found in this study. No significant difference ($p>0.05$) in ERI as compared with other determinants of rHuEPO resistance in patients in quartile 4 was observed in this study.

Table 10: Erythropoietin resistance index quartiles.

Quartile 1	Quartile 2	Quartile 3	Quartile 4
<0.03	0.03 – 0.0435	0.0436 – 0.0713	>0.0713

Table 11: Determinants for rHuEPO resistance in patients with quartile 4 (ERI > 0.0713): univariate analyses.

Characteristic	RR	95%CI		P value [a]
Age (year)	1.007	0.969	1.046	0.730
Sex (male)	1.253	0.418	3.755	0.688
Duration of Dialysis (year)	*0.694*	*0.501*	*0.960*	*0.028*
Ex-smoker (%)	0.675	0.219	2.078	0.493
BMI (kg/m^2)	*0.713*	*0.583*	*0.872*	*0.001*
History of DM (%)	2.4	0.610	9.449	0.211
Pulse Rate (bpm)	0.987	0.946	1.030	0.548
Laboratory Parameters				
CRP (µg/ml)	1.008	0.982	1.035	0.531
Albumin (g/dl)	*0.549*	*0.323*	*0.931*	*0.026*
Urea (mg/dl)	1.007	0.994	1.020	0.275
Creatinine (mg/dl)	1.137	0.836	1.548	0.413
Glucose (mg/dl)	0.990	0.968	1.013	0.405
Dialysis Efficacy				
Kt/V	0.718	0.195	2.644	0.619

[a] : Binary logistic regression
RR : Relative Risk
DM : Diabetes Mellitus

4. Discussion

Anemia and resistance to rHuEPO therapy contributes to the excess morbidity and mortality that associated with ESRD. Treatment with rHuEPO therapy has had a major impact on the clinical outcomes and quality of life of these patients and is a major cost for the suppliers of care. As previously stated, EPO production is markedly reduced in patients with ESRD, resulting in the development of renal anemia, and the use of rHuEPO in ESRD patients results in significant elevation in hemoglobin concentrations and improvements in quality of life for the majority of these patients[18]. Globally approximately 5-10% of ESRD patients receiving

rHuEPO therapy; however, appear to be hypo-responsive to this drug[19].

The present study showed that hemoglobin level in patients with CKD was significantly reduced as compared with normal healthy subjects. Such finding was seen by others[20,21]. Deficiency of EPO, as occurs in CKD patients, retards RBCs maturation from progenitor cells into normoblasts and reticulocytes. In addition to that, EPO deficiency decreases the survival of these immature RBCs, a process known as neocytolysis, thereby resulting in anemia[22]. In the absence of other causes, anemia due to deficiency of EPO is often normocytic and normochromic, implying a reduction in quantity rather than quality of these cells[22].

Because of this low level of hemoglobin that measured in CKD patients, the current study also evaluated the dose of rHuEPO (MPGE-β) that had been given to these patients through-out the study and a significant initial dose adjustment ($p<0.001$) had been made in these patients at the first follow-up as compared with their baseline dose. This dose adjustment became non-significant ($p=0.667$) at the second follow-up. These dose adjustments were done according to KDIGO guideline.

Regardless of these dose adjustments, the present study showed a non-significant change in hemoglobin levels in patients group through-out the study and this may be attributed to the cyclic fluctuations in hemoglobin levels in rHuEPO-treated hemodialysis patients. It was noted that during the treatment of CKD patients on maintenance hemodialysis with rHuEPO, the level of hemoglobin have a great fluctuation, *i.e.* the hemoglobin levels tends to rise or fall in a cyclic pattern and this pattern was different for each patient[5].

As reported in this study, 51.4% of the patients were adequately responding to rHuEPO therapy while the remaining 48.6% were inadequately responding to therapy. Among mechanisms that suggest that rHuEPO therapy is ineffective in some CKD patients is due to the lack of responsiveness to the erythropoietic action of rHuEPO. The underlying causes of this rHuEPO hypo-responsiveness seem to be associated with inflammation and oxidative stress which are common in CKD patients and can be exacerbated by other comorbidities including diabetes mellitus, infections and autoimmune disorders[23].

It is considered that the most appropriate parameter to assess the anemia and its response to rHuEPO treatment is the ERI as observed in several studies[24-28]. The current study showed that ERI in CKD patients who exhibit good response to rHuEPO therapy was significantly lower ($p<0.001$) than that observed in patients with hypo-response to therapy with rHuEPO (0.030 µg/kg/week/g versus 0.0605 µg/kg/week/g respectively). Depending on the result of ROC analysis in this study, an ERI value that is less than or equal to (0.0365 µg/kg/week/g) can be considered as a novel ERI cut-off value in Iraqi CKD patients on maintenance hemodialysis rather than global value of 0.020 µg/kg/week/g[13]and any CKD patients in Iraq with an ERI value >0.0365 µg/kg/week/g hemoglobin or >7.3 U/kg/week/g hemoglobin may have resistance to rHuEPOs therapy.

Viga *et al.* found that the mean ERI and hemoglobin levels at baseline and at 6 months in the 30 CKD patients treated with MIRCERA® and in another 30 CKD patients treated with epoetin-β and darbepoetin-α were not statistically significant[27]. While Mallick et al. reported that the mean ERI for the entire study population of 1305 CKD patients on hemodialysis was 15 ± 14.1 U/kg/week, and males had a significantly lower ($p< 0.001$) value (13.5 ± 13.2 U/kg/week) than females (17.0 ± 14.8 U/kg/week)[28].

Recognition of the rHuEPO hypo-responsive in CKD population is considered of great clinical importance, as this population is unlikely to benefit from any elevation in rHuEPO dosage while remaining at greater risk of adverse events. However, the diagnosis of rHuEPO hypo-responsiveness requires exclusion of other factors associated with anemia resistance such as iron, folic acid or vitamin B_{12} deficiency, hemolysis, aluminum toxicity, malignancies and others[23].

Also this study developed a prediction model for rHuEPO resistance with easily obtainable clinical parameters and routinely collected laboratory variables. The most important factors that influenced ERI in this study were duration of dialysis, body mass index (BMI) and serum albumin. Of note, dialysis efficacy or Kt/V did not significantly influence ERI. These results confirm the findings of Lòpez-Gòmez *et.al.* as they reported that higher BMI was associated with a more favorable response to rHuEPO treatment. Moreover, patients with serum albumin level below 35 g/l had a mean ERI that was higher than mean ERI observed in those patients with serum albumin above 40 g/l. In addition, no significant correlations was found between single-pool Kt/V and ERI ($r=0.024$)[29]. Đurić et.al. reported that patients with the longest duration of hemodialysis (hours) had significantly lower resistance to rHuEPOs applied, which could be a possible explanation for their lowest average dose of rHuEPOs[30].

Nutritional status can play a fundamental role in the clinical course of CKD patients on hemodialysis. Malnutrition is strictly related to inflammation and arteriosclerosis, and through common mediators such as interleukin-6 or tumor necrosis factor-α, it may play a relevant role in EPO resistance[29]. The data of this study corroborate this finding, as patients with a lower body mass index had a higher ERI. Although these findings can be interpreted as a mathematical artifact because the body weight is a factor in calculating ERI, it was believed that this association had clinical significance and may be part of the "reverse epidemiology" described in dialysis patients[29].

Although albumin concentration can be considered as a marker of nutritional status, it is principally a marker of inflammation, which acts as a negative acute phase reactant[29]. In a study of Lòpez-Gòmez et.al., the intensity of the response to rHuEPO was directly related to albumin concentration, and a reduction in albumin level is usually accompanied by an increase in ERI. This situation means that underlying inflammatory processes can be ruled out asthe cause of rHuEPO resistance[29].

This study also reported a favorable effect of longer duration of hemodialysis on anemia correction considering the fact that the values of ERI were lower in patients with longer duration of hemodialysis treatment. The reason for this favorable effect of longer duration of dialysis on anemia is probably multifactorial. It is possible that longer hemodialysis leads to an increase in the clearance of middle molecules including the inhibitors of erythropoiesis[30].

Some studies had shown that lower Kt/V values are associated with higher doses of rHuEPO[29], results of this study do not confirm it, although it is important to note that mean Kt/V in patients was high (1.26 ± 0.41) and only few patients had lower levels of Kt/V than those currently recommended. A possible explanation for this is that the Kt/V was calculated from the dialysis machine directly rather than from Daugirdas formula.

5. Conclusion

In conclusion, easilyavailable clinical parameters and routine laboratory parameters can predict hypo-responsivenessto rHuEPO therapy in hemodialysis patients, and the most appropriate parameter to assess the anemia and its response to rHuEPO treatment is the erythropoietin resistance index.Multivariate models of analysis are required with stepwise inclusion of significant predictors that were determined in this study.

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8. Conflict of interest

None declared.

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