Resistance to Erythropoiesis Stimulating Agents in Children Receiving Renal Replacement Theraphy

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Research Article

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Abstract

Background

The incidence of anemia increases with the stage of chronic kidney disease (CKD). Erythropoietin (EPO) deficiency is the common cause of anemia in CKD. Erythropoietin-stimulating agents (ESAs) are the mainstay of treatment. Sometimes, treatment is challenging due to erythropoietin resistance (ER), which can be assessed using the erythropoietin resistance index (ERI). In this study, our aim was to investigate the factors contributing to high ERI levels in children receiving renal replacement therapy (RRT).

Materials and Methods

Thirty-three children receiving hemodialysis (HD) or peritoneal dialysis (PD) for at least three months were included in this study. Demographic characteristics, laboratory parameters, blood pressure findings, and medication records were documented. The Erythropoietin Resistance Index was calculated by determining the ratio of the weekly EPO dosage adjusted for body weight to the hemoglobin (Hb) level.

Results

The mean ERI value was 15.7 IU/kg/w/g/dL. There was a significant association between serum phosphorus levels and ERI ($p = 0.016$, $r = 0.41$). Mean parathormone (PTH) level was also higher in the high ERI group (599 ± 351 vs 392 ± 320 pg/ml, p: 0.088). An association, close to the statistical significance, was present between ERI and hypertension ($p = 0.06$, $r = 0.32$).

Conclusion

Our study demonstrated a potential relationship between hyperphosphatemia, possibly secondary hyperparathyroidism, and ERI in children receiving RRT. Additionally, the association of hypertension and ERI should not be ignored.

Introduction

Anemia is one of the most important causes of morbidity in CKD. Generally the decline in Hb level is related with the decline of glomerular filtration rate (GFR). According to the Kidney Disease Improving Global Outcomes (KDIGO), risk and severity of anemia depends on the stage of CKD, with a prevalence of 73% at stage 3, 87% at stage 4, and > 93% at stage 5 [1, 2].

Anemia is associated with a variety of adverse clinical consequences, including an increased risk for hospitalization and mortality, and the development and progression of cardiovascular disease, including left ventricular hypertrophy (LVH) [3]. Thus, it is important to diagnose and treat the patients for anemia. According to the KDIGO 2012 guideline, anemia can be diagnosed in children aged over 15 years with CKD when the Hb concentration is less than 13.0 g/dL in males and less than 12.0 g/dL in females. For children aged 0.5 to 5 years, anemia can be diagnosed if the Hb concentration is less than 11.0 g/dL, for children aged 5 to 12 years, if it is less than 11.5 g/dL, and for children aged 12 to 15 years, if it is less than 12.0 g/dL. [4].

The major causes of anemia in CKD can be listed as EPO deficiency, iron deficiency, reduced red blood cell survival and uremic toxicity. Erythropoiesis stimulating agents are the mainstay of the therapy. Unfortunately, in some cases we can not achieve targeted Hb levels with adequate doses or increased ESA doses are required to maintain targeted Hb levels which is called ESA resistance or EPO hyporesponsiveness. Deficiencies of iron (Fe) and vitamins, bleeding, infections, secondary hyperparathyroidism (SHPT), uremia, inadequate dialysis are some of the factors related with EPO hyporesponsiveness [5]. EPO hyporesponsiveness can be assessed by ERI [6]. In the current era, numerous studies have predominantly focused on adult patients, with a primary emphasis on relevant risk factors and the association between EPO hyporesponsiveness and cardiovascular mortality. These studies have consistently demonstrated a significant relationship between ERI and cardiovascular mortality. Authors have indicated that higher levels of C-reactive protein (CRP), alkaline phosphatase (ALP), ferritin, as well as lower levels of albumin and creatinine, may influence EPO hyporesponsiveness [5, 7].

There are very few studies on this subject conducted in childhood. One of these studies was carried out by Pınarbaşı et al., including 100 children who were receiving PD at least one year. In this study, young age was identified as the most important parameter related with ERI. The absence of the residual kidney function, multiple hospitalizations and use of angiotensin-converting-enzyme inhibitors (ACEI) were also detected as important variables affecting the ERI [8]. However these studies are quite inadequate and further studies about relevant risk factors causing EPO hyporesponsiviness in children are needed. In this paper, we aimed to analyse the incidence and related risk factors of ESA hyporesponsiveness in children receiving RRT in our unit.

Materials and Methods

Patients and study design

This is a cross sectional cohort study conducted in Pediatric Nephrology Clinic of Marmara University Hospital in Istanbul. Thirty-three clinically stable patients with end stage kidney disease (ESKD) (14 males, 19 females) receiving HD or PD were evaluated.

Inclusion criteria:

- Diagnosed as CKD and receiving RRT (HD or PD) at least for three months.
- Agreement to participiate in the study
- Being < 18 years old

Exclusion criteria:

- Refusal to participiate in the study

The study was approved by the Ethics Committee of Marmara University Hospital (09.2021.431). The written informed consents were obtained from all participants parents.

Data collection

We recorded the demographic data of the patients, which encompassed age, gender, weight, duration of dialysis, duration of follow-up, primary diagnosis of the patients, medications, presence of hypertension, and the type and treatment dose of recombinant human erythropoietin (rHuEPO). We also evaluated serum Hb, Fe, ferritin, total iron binding capacity (TIBC), folic acid, vitamin B12, platelet, white blood cell (WBC), PTH, calcium (Ca), phosphorus (P), magnesium (Mg), ALP, 25-(OH) vitamin-D and albumin levels, which are routinely evaluated in the follow-up of the patients. Transferrin saturation index (TSAT) was calculated by the ratio of serum iron/TIBC. Blood pressure was recorded in every clinic visit in supine position after the patients have at least 15 minutes rest.

Body fluid volume (overhydration) was measured by bioimpedance spectroscopy by body composition monitor (BCM) with a constant current of 50 kHz. Measurements were performed before dialyses sessions in HD patients. Patients were in supine position and electrodes were placed on the sides without vascular access. In upper extremities, proximal electrode was placed on de dorsal face of wrist and distal electrode was placed on the third metacarpal bone. In lower extremities proximal electrode was placed on the anterior aspect of the ankle, and the distal electrode was placed on the dorsal aspect of the third metatarsal bone. Body composition monitor is a volume model which describes the electrical conductance in a cell suspension, enabling the total body water and extracellular water as well as the intracellular water to be calculated [9].

EPO hyporesponsiveness was evaluated at the last visit by ERI calculated by the ratio of weekly EPO dosage adjusted to body weight and the Hb level (6). Subsequently, we analysed the correlations between ERI and all the parameters associated with CKD. We also categorised patients into two groups by the mean value of the ERI as high ERI group (> 16) and low ERI group (< 16). We than conducted a comparison of parameters between these two groups.

Study outcome

We aimed a Hb level of 11–12 mg/dl, ferritin level > 100 ml/ng and TSAT> %20. Patients received enteral or parenteral Fe preperations. We initiated EPO treatment when the Hb level was below 10 g/dL and adjusted the dosage based on Hb levels during

follow-up visits. The primary objective of this study is to identify the risk factors contributing to EPO hyporesponsiveness in children undergoing RRT.

Statistical analyses

All data were analyzed using the Statistical Packages for the Social Sciences (SPSS Inc., Chicago, IL, USA) 23.0 package. Normality was assessed using the Kolmogorov-Smirnoff test. Results are expressed as mean with standard deviation (mean ± SD) in case of normal distribution and median (interquartile range) in case of non-normal distribution. Differences between data were evaluate using T-test and Mann-Whitney non-parametric U test in normal distribution and non-normal distribution, respectively. Categorical variables were expressed in terms of frequency and percentage, and compared with the chi-square test. Pearson or Spearman correlation tests were used to analyze the correlations between ERI and other clinical indicators. Correlation coefficient r was used to examine the relationship. For all analyses, a p value of < 0.05 was considered statistically significant.

Results

A total of 33 patients with ESKD were enrolled in the study, comprising 13 patients (39.3%) on HD and 20 patients (60.7%) on PD. The age of the patients ranged from 0.82 to 18 years, with a mean age of 5.49 years. Among them, 14 were males (42.4%), and 19 were females (57.6%). The median follow-up time for the patients was 3.1 years (with a range of 6.7 years), and the median duration of dialysis was 2.1 years (with a range of 3.7 years) (Table 1). The causes of ESKD were hypodysplasia in six patients, focal segmental glomerulosclerosis in four patients, neurogenic bladder in three patients, cystinosis in two patients, nephrophitisis in two patients, Joubert syndrome in two patients, hemolitic uremic syndrome (HUS) in two patients, posterior uretral valve (PUV) in two patients, Alport syndrome in one patient, diffuse mesangial sclerosis (DMS) in one patient, Wilms tumor in one patient, primary hyperoxaluria in one patient, autosomal recessive polycystic kidney disease (ARPKD) in one patient and vesicoureteral reflux (VUR) nephropathy (solitary kidney) in one patient (Table-1).

Table 1
Baseline characteristics of the patients

Age, years	**0.82-18 ± 5.49**
Sex, n (%)	19 (%57.6)
Girls	14 (%42.4)
Boys	
•Duration of follow-up, years, median (IR)	3.1 (6.7)
•Duration of dialysis, years, median (IR)	2.1 (3.7)
Type of RRT	20 (60.7%)
PD, n (%)	13 (39.3%)
HD, n (%)	
Diagnosis	6 (%18.1)
Hypodysplasia, n (%)	4 (%12.1)
FSGS, n (%)	3 (%9)
Neurogenic bladder, n (%)	2 (%6)
Cystinosis, n (%)	2 (%6)
Nephronophitisis, n (%)	2 (%6)
Joubert syndrome, n (%)	2 (%6)
HUS, n (%)	2 (%6)
PUV, n (%)	1 (%3)
Alport Syndrome, n (%)	1 (%3)
DMS, n (%)	1 (%3)
Wilms tumor, n (%)	1 (%3)
Primary hyperoxaluria, n (%)	1 (%3)
ARPKD, n (%)	1 (%3)
VUR Nephropathy(solitary kidney), n (%)	4 (%12.1)
Others, n (%)	
Types of ESA used	22(%66.6)
Epoetin alfa, n (%)	11 (%33.4)
Darbepoetin alfa, n (%)	
Use of ACEIs, n (%)	12(%36.3)

Parameters which have homogeneous distrubution are presented by mean values and standart deviations, •Parameters which have non homogeneous distrubution are presented by median values (interquarter range). RRT, renal replacement theraphy; PD, peritoneal dialysis; HD, hemodialysis; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; PUV, posterior urethral valve; DMS, diffuse mesangial sclerosis; ARPKD, autosomal recessive polycystic kidney disease; VUR, vesicoureteral reflux; ESA; erythropoiesis stimulating agent, ACEIs, angiotensin- converting enzyme inhibitors

The mean ERI value was 15.7 IU/kg/w/g/dL. All patients were categorised into the low ERI group (ERI ≤ 16 IU/kg/w/g/dL) and the high ERI group (ERI > 16 IU/kg/w/g/dL) based on the mean ERI value. Among the patients, 22 (66.6%) received epoetin alfa, and 11 (33.4%) received darbepoetin alfa (Table 1). In the low ERI group, 14 patients received epoetin alfa, while three patients received darbepoetin alfa (a ratio of 4.6:1). In the high ERI group, eight patients received epoetin alfa, and eight patients received

darbepoetin alfa (a 1:1 ratio). This was statistically significant with a p value of 0.049 (Table-2). However, in correlation analysis, we did not demonstrate a significant association between ERI and EPO subtypes (p = 0.18) (Table-3). The mean Hb value was 10.47 mg/dl and was lower in high ERI group (p:0.00) (Table-2). Hb concentration exhibited a negative correlation with ERI (p = 0.00, r=-0.75) (Table-3). There was no significant difference between WBC, platelet, Fe, TSAT, TIBC, folic acid, vitamin B12 levels and ERI groups (p > 0.05) (Table-2). The mean albumin level was lower in low ERI group compared to high ERI group, it was not statistically significant (3.93 ± 0.13 and 5.28 ± 1.65 respectively, p = 0.367) (Table-2). CRP levels were negative in all patients.

The mean serum phosphorus levels were significantly higher in the high ERI group compared to the low ERI group (6.61 ± 1.67 vs. 5.14 ± 1.14 mg/dL, respectively, p = 0.007) (Table 2). Furthermore, correlation analysis revealed a significant positive association between serum phosphorus levels and ERI (p = 0.016, r = 0.41) (Table 3). The mean PTH levels were higher in the high ERI group, approaching statistical significance (599 ± 351 vs. 392 ± 320 pg/mL, p = 0.088). Mean calcium levels were lower in the high ERI group compared to the low ERI group, although this difference did not reach statistical significance (7.66 ± 0.96 vs. 9.54 ± 0.27, p = 0.263, respectively)

Table 2
Comparison of demographic, clinical and biochemical characteristics of patients with high and low ERI groups

Variables	Overall (n:33)	Low ERI Group (n:17)	High ERI Group (n:16)	*p value
ERI (IU/kg/w/g/dL)	15.7 ± 6.7	< 16	> 16	
Age (years)	10.7 ± 5.5	12 ± 4.7	9.4 ± 6.1	0.18
Sex (male/female) (%)	14(42.4%)/19(57.6%)	8/9	6/10	0.57
•Duration of dialysis (years)	2.1 (3.7)	2.1(4.3)	3.1 (3.9)	0.27
•Duration of follow-up (years)	3.1 (6.7)	2.84 (7.7)	3.15 (4.9)	0.95
BMI (kg/m2)	16.9 ± 2.6	17.5 ± 3.1	16.3 ± 1.7	0.17
Hb (mg/dl)	10.5 ± 1.6	11.6 ± 1.2	9.2 ± 1.1	**0.00**
WBC (×109)	6882.8 ± 2723.4	6647 ± 2771	7132 ± 2739	0.61
•PLT (×109)	264.000 (137.000)	252.000 (108.250)	354.000 (133.000)	0.22
•Ferritin (ml/ng)	335.6 (416.5)	382.5 (273.00)	329.4 (517.80)	0.74
•Fe (mg/dl)	84 (41.5)	88.5 (41.7)	84.4 (52.2)	0.84
TIBC (mg/dl)	247.2 ± 56.2	263.8 ± 50	229.6 ± 58.6	0.82
•TSAT (%)	30.5 (20.7)	30.5 (14.7)	30 (32.5)	0.33
•Folic acid (nmol/L)	7 (10.6)	6.4 (9.6)	7.4 (14.4)	0.86
•Vitamin B12 (pg/ml)	457 (518)	432 (812)	580 (389)	0.46
•Albumin (gr/dl)	3.8 (1)	3.9 (0.7)	3.6 (1.6)	0.36
median	4.5 ± 4.6	3.9 ± 2.6	5.3 ± 6.6	
mean				
PTH(pg/mL)	493.1 ± 346.8	392 ± 320	599 ± 351	**0.08**
•ALP (U/L)	199 (219.5)	168 (210)	263.5 (257.5)	0.48
P (mg/dl)	5.8 ± 1.5	5.1 ± 1.1	6.6 ± 1.7	**0.007**
•Ca (mg/dL)	9.5 (1.1)	9.5 (1.1)	9.4 (1.6)	0.26
median	8.6 ± 2.9	9.5 ± 1.1	7.6 ± 3.8	
mean				
•Vitamin 25-(OH) D3 (ng/ml)	25 (16.7)	28.5 (19.9)	21.8 (13.8)	0.34

Parameters which have homogeneous distrubution are presented by mean values and standart deviations,

•parameters which have non homogeneous distrubution are presented by median values (interquarter range).

*Significant difference between the low ERI group and the high ERI group, $p < 0:05$. ERI: erythropoietin

resistance index; BMI: body mass index; Hb: serum hemoglobin concentration; WBC: white blood cell count;

PLT: platelet count; Fe: serum iron level; TIBC: total iron binding capacity; TSAT: transferrin saturation;

PTH: serum parathyroid hormone; ALP: serum alkaline phosphatase; P: serum phosphorus; Ca: serum

calcium; LVH: left ventricular hypertrophy; ACEIs: anjiotension converting enzyme inhibitors; EPO: erythropoietin

Variables	Overall (n:33)	Low ERI Group (n:17)	High ERI Group (n:16)	*p value
Magnesium (mg/dl)	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.4	0.92
Hypertension (n) (%)	22/33 (66.6%)	9/17 (52.9)	13/16 (81.2)	**0.085**
≥ 2 antihypertensive drugs; (n)	12/22	5/9	7/13	0.89
Use of ACEIs; (n) (%)	12/33 (36.3)	5/17 (29.4)	7/13 (53.8)	0.39
EPO subtypes (epoetinalfa/darbepoetin alfa) (n)	22/11	14/3	8/8	**0.049**
•Overhydration (liter/kg)	0.01 (0.9)	0.1 (2.1)	0.01 (0.04)	0.78
LVH (n) (%)	15/33 (45.4)	6/17 (35.2)	9/16 (56.2)	0.22
Parameters which have homogeneous distrubution are presented by mean values and standart deviations,				
•parameters which have non homogeneous distrubution are presented by median values (interquarter range).				
*Significant difference between the low ERI group and the high ERI group, $p < 0:05$. ERI: erythropoietin				
resistance index; BMI: body mass index; Hb: serum hemoglobin concentration; WBC: white blood cell count;				
PLT: platelet count; Fe: serum iron level; TIBC: total iron binding capacity; TSAT: transferrin saturation;				
PTH: serum parathyroid hormone; ALP: serum alkaline phosphatase; P: serum phosphorus; Ca: serum				
calcium; LVH: left ventricular hypertrophy; ACEIs: anjiotension converting enzyme inhibitors; EPO: erythropoietin				

Table 3

Correlations between ERI and parameters ∗The correlation was statistically significant, $p < 0:05$.ERI: erythropoietin resistance index; Hb: serum hemoglobin concentration; WBC: white blood cell count; PLT: platelet count; Fe: serum iron level; TIBC: total iron binding capacity; TSAT: transferrin saturation

	Age	Duration of follow up	Duration of dialyses	Hb	WBC	PLT	Fe	TSAT	TIBC	Ferritin	Folic acid	Vitamin B12	Albumin
ERI r	-0.29	-0.1	0.75	**0.75***	-0.05	0.12	0.09	0.18	-0.26	0.09	0.09	0.10	-0.02
p	0.09	0.58	0.67	**0.00***	0.78	0.49	0.60	0.30	0.13	0.58	0.59	0.57	0.25

	Ca	P	Mg	ALP	Vitamin 25-(OH) D3	PTH	BMI	Overhydration (liter/kg)	HT	LVH	ACEI	EPO subtypes
ERI r	-0.19	**0.41***	0.16	0.15	0.07	0.077	-0.2	-0.15	**0.32***	0.16	0.18	0.23
p	0.27	**0.016***	0.36	0.40	0.67	0.67	0.26	0.39	**0.06***	0.29	0.29	0.18

∗The correlation was statistically significant, $p < 0:05$. ERI: erythropoietin resistance index; BMI: body mass index; PTH: serum parathyroid hormone; ALP: serum alkaline phosphatase; P: serum phosphorus; Ca: serum calcium; HT: Hypertension; LVH: left ventricular hypertrophy; ACEIs: anjiotension converting enzyme inhibitors; EPO: erythropoietin

No significant differences were observed in Mg, ALP and vitamin 25-(OH) D levels ($p > 0.05$) (Table-2). Correlations between ERI and all of the other parameters related to CKD bone mineral disease were also evaluated, no significant correlations were found (Table-3).

The prevelance of hypertension was higher in high ERI group compared to the low ERI group ($p = 0.085$) in the presence of comparable body fluid volumes of two groups (Table-2). An association, close to the statistical significance, was found between ERI and hypertension in correlation analysis, which supports this relationship ($p = 0.06$, $r = 0.32$) (Table-3).

There was no significant correlation between body fluid volume (overhydration) measured by bioimpedance spectroscopy and ERI (p = 0.39). Among the hypertensive patients, twelve of them were using more than one antihypertensive drug, with seven in the high ERI group (Table 2). Left ventricular hypertrophy was identified in 15 out of 33 patients, with six in the low ERI group and nine in the high ERI group; however, this difference did not reach statistical significance (p = 0.227) (Table 2). Of the patients, 12 (36.3%) received ACEIs, with five in the low ERI group and seven in the high ERI group; however, this was not statistically significant (p = 0.39) (Table 2), and there was no significant correlation between ERI and the use of ACEIs (p = 0.29) (Table-3).

Discussion

Our study revealed that hyperphosphatemia and hypertension are associated with Erythropoietin (EPO) hyporesponsiveness in children undergoing RRT. Additionally, we found that epoetin alfa was more frequently used than darbepoietin alfa in the low ERI group compared to the high ERI group. This difference was statistically significant; however, no significant association was observed in the correlation analysis.

In 2006 Dicjens et al. demonstrated a positive association between ERI and hyperphosphatemia [13]. The potential mechanism underlying EPO resistance induced by hyperphosphatemia may involve several factors: the downregulation of EPO receptors (EPOR) due to hyperphosphatemia's impact on shifting the oxygen-hemoglobin dissociation curve to the right, thereby facilitating increased oxygen delivery to tissues; direct downregulation of EPOR itself, potentially as a result of inflammation; its influence on acidosis, attributable to the presence of H + ions in its serum form; and its relationship with SHPT [12, 13, 14]. We also observed that, although not statistically significant, the mean PTH level was higher, and the mean calcium level was lower in the high ERI group compared to the low ERI group, which lends support to a potential relationship between secondary SHPT and ERI. Numerous studies have demonstrated a significant association between SHPT and anemia in patients with CKD. The suspected mechanisms of anemia in SHPT include the suppression of endogenous EPO production by PTH, myelofibrosis, and reduced red blood cell survival and production. [9–11]. Additonally, elevated fibroblast growth factor 23 (FGF23) level which is a parameter of SHPT, can lead to chronic inflammation, contribute to anemia and EPO resistance in these patients [12].

Hypertension is a well-known side effect of ESA therapy. Vascular endothelial cells and smooth muscle cells have erythropoietin receptors on their walls. One of the suspected mechanism of hypertension in patients undergoing ESA therapy is vasoconstriction due to presence of these receptors [17]. Changes in blood volume and blood viscosity also plays a role in hypertension induced by ESA therapy [18]. According to the literature, increased endothelin-1 concentration, thromboxane A2 release and decreased nitric oxide and prostocyclin levels have potential effects [19–22]. In the review written by Susanne et al., renin-angiotension system is idenified as another potential cause of hypertension and the use of ACEİ/ARBs are recommended to control hypertension [17]. In contrast, there are several studies demonstrating that ACEİ/ARBs inhibit erythropoiesis induced by rHuEPO and induces erythropoietin resistance [23, 24]. In our study, the presence of hypertension was more prevelant in high ERI group than low ERI group in the presence of comparable body fluid volumes of two groups. Correlation analysis revealed an association, close to the statistical significance between ERI and hypertension, which supports this relationship. There was not a significant correlation between ERI and use of ACEIs. Therefore, it is advisable to closely monitor children receiving ESA theraphy for hypertension.

Darbepoetin alfa exhibits a significantly longer elimination half-life and lower clearance compared to epoetin alfa, resulting in a prolonged erythropoietic effect [15]. In 2014, Arrieta et al. demonstrated that darbepoetin alfa maintains Hb stability and reduces ERI levels more effectively than epoetin alfa [16]. We administered two types of ESA for treatment of anemia in our patients. While the majority of patients in the low ERI group used epoetin alfa in our study, we did not demonstrate a significant relationship between ERI and EPO subtypes in correlation analyses.

There are several studies exploring various risk factors associated with ERI. Carnitin deficiency, treatment with intravenous vitamin B6 treatment, elevated high thyroid-stimulating hormone levels, oxidative stres and malnutrition have all been found to be significantly related with high ERI levels [25–30]. In a cross-sectional study conducted by Hara et al., anti erythropoietin receptor antibodies were identified as a significant risk factor for EPO hyporesponsiveness after adjusting for potential confounders [31]. Treatment by continuous erythropoietin receptor activators could achieve successful anemia control and low ERI values [32]. A study supporting this hypothesis and investigating genetic polymorphisms was conducted by Kao et al. in 2021. They explored store-operated calcium channel (SOC) signaling, one of the pathways activated by erythropoietin. Their study revealed a significant

relationship between high ERI levels and single nucleotide polymorphisms in Stromal Interaction Molecule-1(STIM1) and Calcium Release-Activated Calcium Modulator-1 (ORA1). They further demonstrated that SOC1-mediated calcium signaling plays a crucial role in erythropoietin resistance [33]. Polimorphsims of ACE and interleukin-6 were also been associated with high ERI levels [33]. Another possible mechanism underlying ESA resistance is dialysis inadequency. There are several studies conducted in this era revealing that inadequate dialysis can lead to ESA resistance [8, 34].

This study has several limitations. First, it has a relatively small sample size. Another significant limitation is that the ERI level was calculated only once, and its changes over time could not be evaluated together with the alterations in other parameters. Furthermore, we did not evaluate other risk factors affecting ERI such as carnitine deficiency, vitamin B6 treatment, dialyses aduquency and genetic polymorphisims, among others. Despite these limitations, our study also exhibits noteworthy strengths. To the best of our knowledge, it is one of the rare studies conducted on children and involves both HD and PD patients. It is well designed and the relationship of ERI and other parameters has been statistically evaluated using several different ways. To gain a more comprehensive understanding of the risk factors associated with ERI, prospective studies with larger sample sizes are warranted. These studies should assess all relevant risk factors, especially dialysis adequacy, by calculating ERI at multiple time points.

Conclusion

Erythropoietin resistance is a significant risk factor for cardiovascular morbidity and all-cause mortality. It is essential to assess risk factors and prevent ER. Our study demonstrates that hyperphosphatemia is the most critical factor influencing ER in children. Additionally, hypertension and the type of erythropoiesis-stimulating agent are other important variables that may be linked to ER.

Declarations

Authors declare they have no financial or non-financial interests.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mehtap Kaya, Neslihan Cicek and Sercin Guven. The first draft of the manuscript was written by Mehtap Kaya. Reviewing, editing and supervision was performed by Ibrahim Gokce and Harika Alpay. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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